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Interactions between Diatoms and Bacteria

Shady A. Amin, Micaela S. Parker, and E. Virginia Armbrust
School of Oceanography, University of Washington, Seattle, Washington, USA

INTRODUCTION

The oceans represent the largest biome on Earth. Bacteria, archaea, and protists comprise the majority of biomass in the ocean. The ubiquity and abundance of these microbes mean that they drive oceanic biogeochemical cycles (54), which in turn impact microbial biodiversity and community-level interactions (170). A defining characteristic of the marine environment is that both compounds and organisms are relatively scarce. Microbial densities in the oceans (10^5 to 10^6 cells per gram of seawater) are orders of magnitude less than those found in sediments (10^8 cells/g), humans (10^{14} cells/g), or soil (10^9 cells/g) (157, 159, 185). Despite such low average densities where diffusion of cells and molecules is rapid, microbes are concentrated in microscale patches throughout the oceans (11, 21, 68). Stratification and hydrodynamic shear also create thin layers and macroscale patches of microbes that can extend for kilometers (17, 52, 64). The close proximity of microbes in these patches and the heterogeneous distribution of these patches in the ocean suggest that microbes interact across multiple spatial scales.

Marine ecosystems are constructed around networks that connect every species to many other species at a range of spatial scales, manifested through interactions that include mutualism, competition, and parasitism (53). Interspecies interactions can be hard to observe *in situ* because they are indistinguishable under "equilibrium" conditions, and the system must be either disturbed or observed over long periods to perceive these interactions. Most of our understanding of interspecies interactions comes from terrestrial environments, primarily from microbe-plant or microbe-mammal interactions, where association of bacteria with a "stable platform" facilitates observations. In the ocean, stable platforms for studying these interactions exist in the near-shore/intertidal areas (e.g., kelp beds and coral reefs) or on the seafloor (e.g., hydrothermal vents and sediments). Few comparable stable structures exist for studying microbial interactions that dominate the vast expanses of the pelagic ocean.

In this review, we focus on interactions between two important groups of marine microbes, diatoms and bacteria. Diatoms are ubiquitous photosynthetic eukaryotes that are responsible for about 20% of photosynthesis on Earth (Fig. 1A). They serve as the base of the marine food web when they are consumed by higher eukaryotes, and they can also serve as food for heterotrophic bacteria. Diatoms are encased in distinctive, porous silica shells, called frustules (Fig. 1B), that cause them to sink rapidly when they die, carrying fixed organic carbon to the deep ocean. Therefore, diatoms play a major role in driving the biological pump and shaping the carbon cycle. They also influence the biogeochemical cycles of important elements such as nitrogen, silicon, and iron and thus affect other microbial communities (7). Heterotrophic bacteria are ubiquitous scavengers that utilize organic carbon pro-

Address correspondence to E. Virginia Armbrust, armbrust@u.washington.edu.

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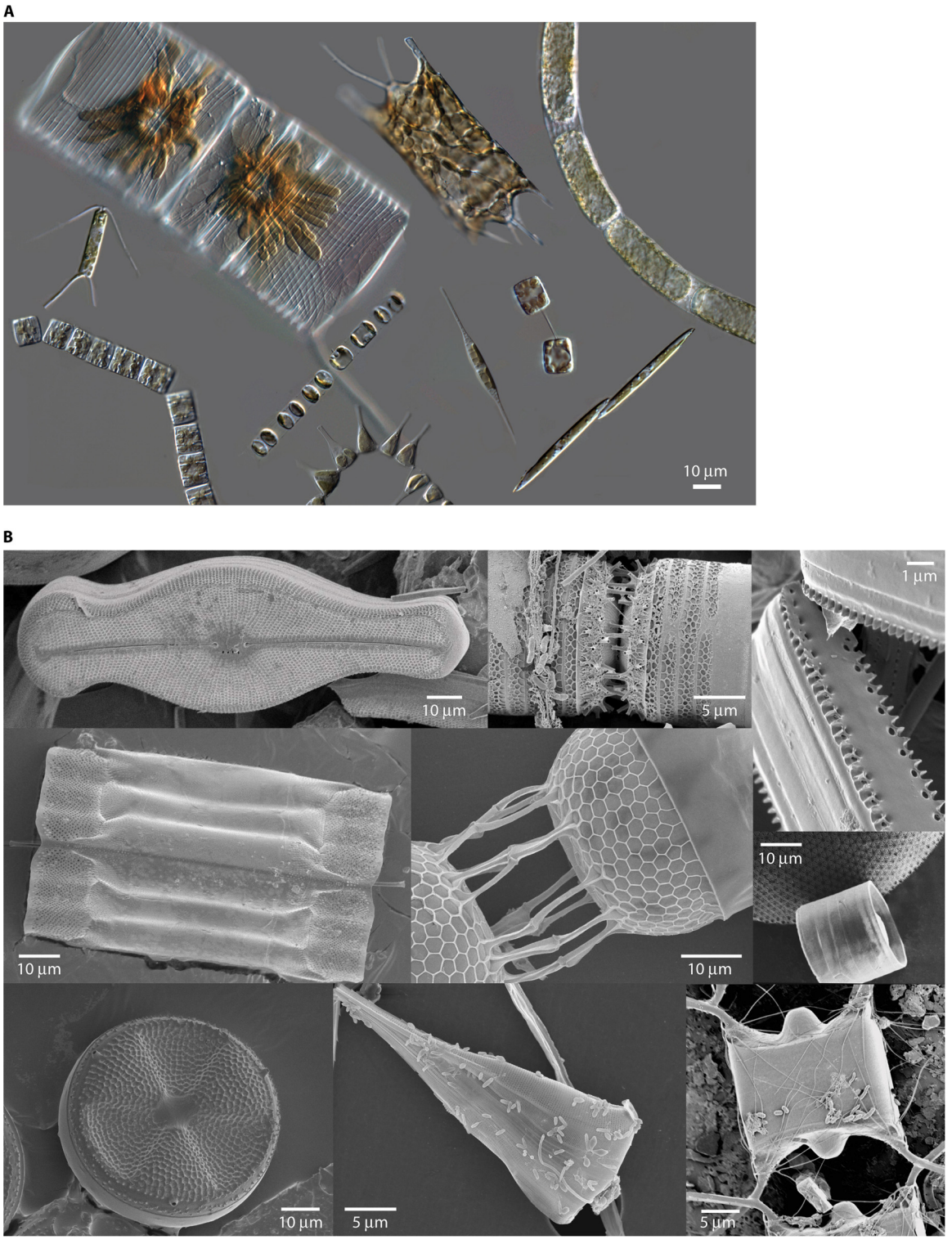


FIG 1 Micrographs of representative diatom species. (A) Light micrographs of diatoms. Clockwise from the top left corner: *Striatella unipunctata*, *Odontella* sp., *Stephanopyxis turris*, *Pseudo-nitzschia* sp., *Thalassiosira* sp., *Cylindrotheca* sp., *Asterionellopsis glacialis*, *Skeletonema costatum*, *Grammatophora oceanica*, and *Chaetoceros* sp. Images are courtesy of Colleen Durkin. (B) Scanning electron microscopy (SEM) images of diatoms. Clockwise from the top left corner: *Didymosphenia geminate* (Lyngbye), valve view; *Lauderia annulata* with bacteria, girdle view showing attachment of two cells; *Thalassionema nitzschioides* (Grunow), valve view showing the rounded valve end; *Coscinodiscus* sp. after sexual reproduction in a culture restored large cells (top) from small gametangial cells (bottom); *Chaetoceros didymus* with bacteria; *Asterionellopsis glacialis* with bacteria; *Actinoptychus senarius*; *Lithodesmium undulatum*, girdle view; and *Stephanopyxis turris* (Greville) (center). Images are courtesy of Julie Koester (*Coscinodiscus* sp.) and Mark Webber (the rest).

duced by diatoms and other autotrophs, thereby remineralizing a large portion of organic matter back to CO_2 (36). Because of their abundance and high functional diversity, marine bacteria drive the biogeochemical cycles of most biologically relevant elements (89).

Diatoms and bacteria have cooccurred in common habitats throughout the oceans for more than 200 million years, fostering interactions between these two groups over evolutionary time scales. Hundreds of genes in diatom genomes appear to have been acquired from bacteria. These acquisitions likely played a major role in the diversity and success of diatoms (8, 24). For example, many of the estimated 784 genes acquired by the diatom *Phaeodactylum tricornutum* from bacteria are involved in nitrogen and organic carbon utilization, cell wall assembly, DNA recombination, and the ornithine-urea cycle (2, 24). The large numbers of genes believed to be transferred from bacteria to diatoms reaffirm the paradigm that diatoms and bacteria have developed specific interactions over hundreds of millions of years.

Understanding interactions between diatoms and bacteria is of prime importance to deciphering oceanic nutrient fluxes and biogeochemical cycles. How can we improve our knowledge of diatom-bacterium interactions? Will climate change break down or further promote these interactions? This review provides a summary of known bacterial associations with diatoms and shows that known diatom-associated bacteria appear to be limited to a few genera. Based on these associations, we discuss the microscopic environment of diatoms and bacteria to illustrate how it affects their encounters. We then review signaling mechanisms for intra- and interspecies communication in the context of structure and perception of signaling molecules that can occur within this microenvironment. Signaling between bacteria and diatoms may help initiate specific interactions. Finally, we discuss known diatom-bacterium interactions, emphasizing technological advances that will help in the discovery of new interactions. Because interactions are mediated by how microbes communicate, deciphering the language of diatoms and bacteria will strengthen our understanding of these groups and how they shape our oceans' biogeochemistry.

DIATOM-ASSOCIATED BACTERIA

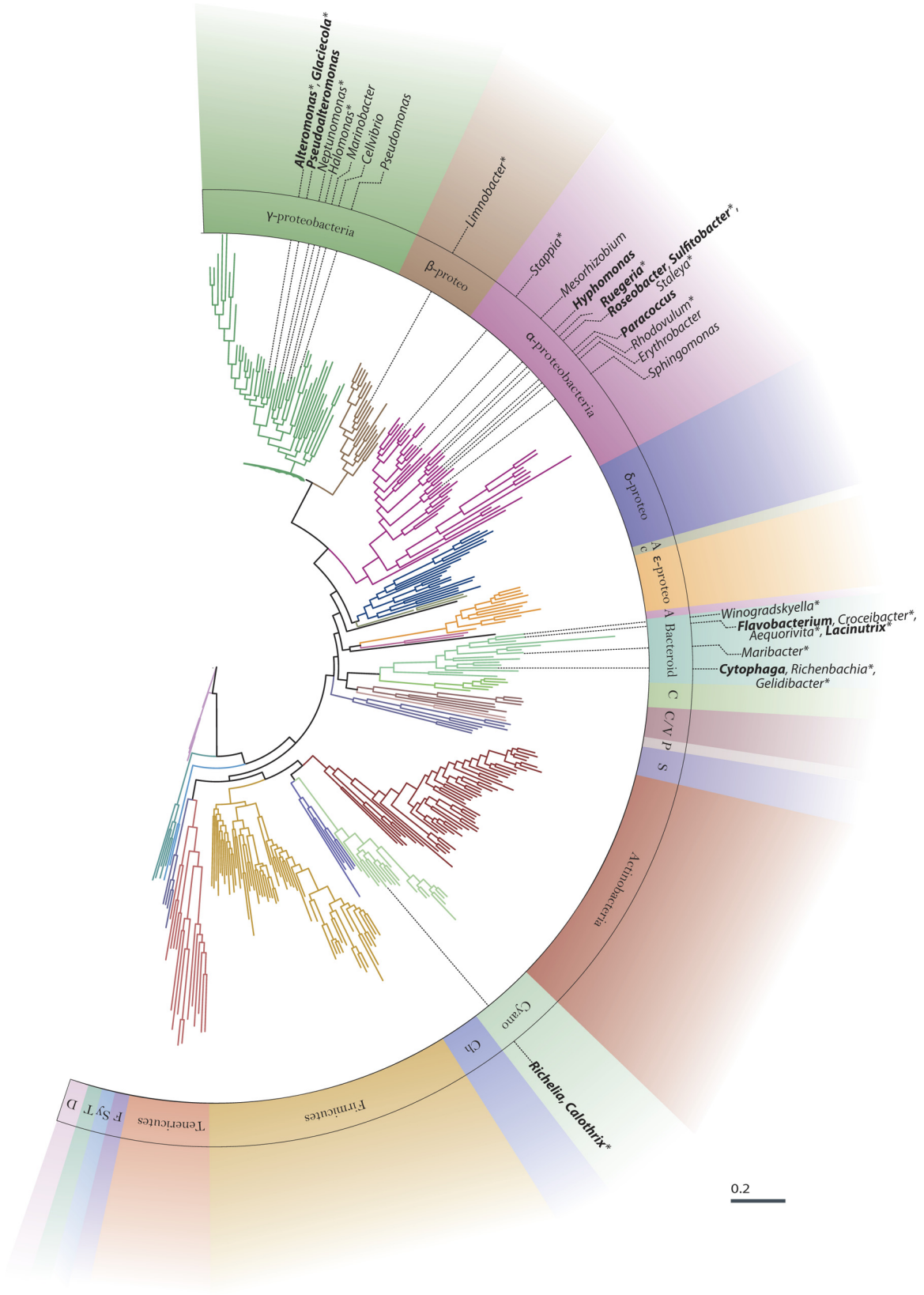
Microbial interactions are at the core of species success or failure. These interactions constitute an important component of microbial communities, where synergism or competition among species can drive the diversity of an ecosystem. The fact that no microbe exists alone in nature means that interactions with other species are required. The "competitive exclusion principle" states that two or more species cannot exist if they are competing for the same resource(s), provided that the system is isotropic (72). This mathematical principle has been challenged since its conception due to the high diversity of most ecosystems studied in nature. A prime example in nutrient-poor oceans is the existence of diverse phytoplankton species that compete for multiple inorganic nutrients yet do not reduce to a single species, a phenomenon known as the "paradox of the plankton." It has been argued that the lack of a true system in equilibrium prevents the existence of constant competition between species (82). Predation and synergism also reduce competition by keeping a balance between species or by recycling limiting resources. These types of interactions can provide further explanation of the paradox of the plankton.

Numerous studies over the past 100 years have shown that marine bacteria are involved in complex interactions with diatoms. Evidence for the ability of marine bacteria to rapidly oxidize algal exudates appears as early as 1933, when bacteria were shown to remineralize exogenous plant and algal material (181). Subsequent studies demonstrated the ability of marine bacteria to remineralize organic matter from the decomposition of dead diatoms to yield their inorganic constituents, particularly phosphorus, nitrogen, and carbon (180). Microbial activity *vis-à-vis* alga-derived organic matter was thought to be limited to dead diatoms and not to include actively growing cells (38, 180). More recent evidence, summarized below, indicates that some bacteria consistently associate with growing diatoms through specific interactions, while other bacteria colonize sinking diatom particles and decompose organic matter therein.

The ability of diatoms to influence bacterial diversity is most readily observed with laboratory isolates. A molecular survey of bacterial diversity from cultures of six nonaxenic diatom genera (*Ditylum*, *Thalassiosira*, *Asterionella*, *Chaetoceros*, *Leptocylindrus*, and *Coscinodiscus*) revealed distinct bacterial phylotypes associated with each genus. Alphaproteobacteria (*Sulfitobacter*, *Roseobacter*, *Ruegeria*, and *Erythrobacter* genera), *Bacteroidetes* and to a lesser extent betaproteobacteria were among the most prominent across all diatoms examined (158) (Fig. 2). 16S ribosomal DNA (rDNA) clone libraries from two species of the diatom genus *Pseudo-nitzschia* shared bacteria belonging to the *Roseobacter* clade (*Roseobacter* and *Sulfitobacter* genera), *Gammaproteobacteria*, and *Bacteroidetes* (66) (Fig. 2). Consistent associations between different geographic *Pseudo-nitzschia multiseries* isolates originating from the Atlantic Ocean and the north Pacific Ocean and specific clades of bacteria belonging to *Alphaproteobacteria* (*Sulfitobacter*), *Gammaproteobacteria* (*Marinobacter*), *Betaproteobacteria* (*Limnobacter*), and *Bacteroidetes* (*Croceibacter*) have been observed (S. A. Amin, unpublished data) (Fig. 2). Numerous other studies examining the bacterial communities of diatom cultures demonstrate that the *Proteobacteria* and *Bacteroidetes* are the main heterotrophic bacterial phyla associated with diatoms. Within these phyla, specific genera (e.g., *Sulfitobacter*, *Roseobacter*, *Alteromonas*, and *Flavobacterium*) appear to be strongly associated with diatoms based on their repeated occurrence in different studies (65, 81, 91, 153–155) (these and other genera found associated with diatoms are highlighted in Fig. 2).

Other studies have examined bacterial community dynamics during diatom blooms or in diatom-dominated phytoplankton communities. For example, a time series over the course of 7 months of bacterial community dynamics and their correlations to phytoplankton showed that *Roseobacter*, *Sulfitobacter*, and members of *Cytophaga* were among the most relevant bacterial genera present whether in the attached (>5-μm) or free-living (5- to 0.22-μm) fractions. In addition, bacterial numbers correlated more strongly with abundance and diversity of diatoms than with other groups of phytoplankton such as dinoflagellates (149). These associations are consistent with previous laboratory surveys of diatom cultures.

This overview of bacterial associations with diatoms indicates that two heterotrophic bacterial phyla, *Proteobacteria* and *Bacteroidetes*, appear to be consistently observed with diatoms and that these bacteria are generally confined to a small number of genera (conserved bacterial associations with diatoms are depicted in Fig. 2). How do these bacteria interact with diatoms to establish such specific associations? We must examine diatoms and bacteria on a scale that is relevant to them to answer this question. Encounters between diatoms and bacteria occur in a confined space that ex-


Alteromonas*, Glaciecola*
Pseudoalteromonas
Neptunomonas*
Halomonas*
Marinobacter
Cellvibrio
Pseudomonas
γ-proteobacteria
Limnobacter*
β-proteo
Stappia*
Mesorhizobium
Hyphomonas
Ruegeria*
Roseobacter, Sulfitobacter*,
Staleya*
Paracoccus
Rhodovulum*
Erythrobacter
Sphingomonas
α-proteobacteria
δ-proteo
ε-proteo
Winogradskyella*
Flavobacterium, Croceibacter*,
Aequorivita*, Lacinutrix*
Maribacter*
Cytophaga, Richenbachia*,
Gelidibacter*
Bacteroid
Actinobacteria
Cyano
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Richelia, Calothrix*
Firmicutes
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hibits characteristics different from those of bulk seawater. The motility and attachment mechanisms of these bacteria are precursors to their interaction with diatoms.

THE PHYCOSPHERE: THE BACKYARD OF DIATOMS

In 1972, Bell and Mitchell coined the term "phycosphere" to describe a region that extends outward from an algal cell, chain, or a colony of cells to some distance "in which bacterial growth is stimulated by extracellular products of the alga" (18). The phycosphere is thus the aquatic analog of the rhizosphere in soil ecosystems and has direct implications for nutrient fluxes to and from algal cells. The phycosphere exists because all aquatic microbes smaller than ~100 μm (smaller than the Kolmogorov scale) are surrounded by a thin layer of fluid known as the diffusive boundary layer. The diffusive boundary layer is not mixed with the surrounding (bulk) fluid because turbulence is not sustainable at such small scales (102). Transport through this layer is entirely diffusive rather than advective. Both theoretical diffusion models and laboratory experiments have been used to understand the role of diffusive boundary layers in algal physiology (9, 95, 122, 125, 134, 135, 138, 145, 187).

The availability of extracellular products within the phycosphere is governed by the physics of the phycosphere and by the ability of bacteria to detect this encounter zone. The simplest scenarios model the phycosphere in the absence of motility or fluid motion, where pure diffusion laws govern the flux of nutrients to and from the microbe. The total flux of a molecule in this instance is proportional to the surface area of the cell, which is directly related to cell size. This can be seen from the equations that govern diffusion of a water-soluble molecule down a gradient (equation 1) and the efflux of a molecule from a spherical object (equation 2):

$$C_r = [Q_D/(4\pi Dr)] + C_\infty \quad (1)$$

$$Q_D = 4\pi D r_0 (C_0 - C_\infty) \quad (2)$$

where C_r is the concentration of the molecule observed at distance r from the cell center (where $r \geq r_0$, the radius of the cell), Q_D is the flux of the nutrient from the cell surface, D is the diffusion coefficient of the molecule, C_∞ is the concentration of the molecule in bulk seawater, and C_0 is the concentration of the molecule at the cell surface (88, 95). Consider a scenario where the concentration of a small organic molecule is 10 μM at the surface of a microbe but rapidly dilutes to a bulk concentration of 10 nM. Within the phycosphere of a 20-μm cell, 10% of the cell surface concentration will extend 90 μm away from the cell surface, whereas this same concentration is reached 18 μm away from the cell surface of a 4-μm cell (Fig. 3A and B). Thus, exuded molecules from larger diatoms extend further away from the cell surface than those from smaller diatoms, and this in turn influences how bacteria detect and interact with these cells.

The more complex scenarios include fluid motion or cell motility, either of which distorts and compresses the diffusive boundary layer around a cell considerably (Fig. 3C and D). Lazier and Mann estimate that for a spherical, motile (or sinking) cell with a 20-μm diameter moving at a velocity of 20 μm/s, a 10% increase in molecular flux will occur due to cell motion (102). Fluid motion can also affect the diffusive boundary layer around cells, though the effect is minor relative to that of cell motility (102).

Diatom-Bacterium Encounters

The dynamic nature of the diffusive boundary layer in the ever-changing fluid environment and the resulting complexity of chemical fluxes that take place near cell surfaces suggest that the phycosphere acts as a hot spot for a mosaic of ongoing interactions between diatoms and bacteria. How do marine bacteria find a phycosphere? Many bacteria are known to find nutrients using chemotaxis, a phenomenon that relies on detection of molecules in the immediate surroundings of a cell to determine swimming direction either toward (attractant) or away from (repellent) a chemical gradient. Motility studies on the model bacterium *Escherichia coli* suggested an average velocity of 30 μm s^{-1} for this species and a run-and-tumble mechanism (random-walk model) (19). Some marine bacteria swim faster than their terrestrial counterparts, attaining speeds of up to 100 to 500 μm s^{-1} (12, 123). In addition, they use a run-and-reverse strategy, rather than the run-and-tumble strategy, which allows them to move greater distances before changing directions, greatly improving their chemotactic response in the dilute marine environment (12, 13, 123, 168). In the presence of motile algae, two species of marine bacteria (*Pseudoalteromonas haloplanktis* and *Shewanella putrefaciens*) increased their swimming speeds relative to those of no-alga controls and made nonrandom turns that allowed them to track algal movement (12). Because these isolates swam faster than algae, they could move in and out of the phycosphere as needed.

An alternative way for bacteria to remain within a phycosphere is to attach to the surface of a diatom. Mechanisms underlying attachment remain unclear, but they likely involve extracellular molecules such as polysaccharides or proteins. Bacterial attachment to living cells in the marine environment has been reported in a number of cases involving a wide range of phytoplankton (20, 62, 90, 91, 121). Possible mechanisms for bacterial attachment to diatoms can be drawn from plant-bacterium symbioses, such as

FIG 2 Maximum-likelihood phylogenetic tree of the bacterial domain, highlighting heterotrophic taxa most commonly found associated with diatoms. Also shown are the autotrophic nitrogen-fixing bacteria (*Cyanobacteria*) known to be associated with diatoms. Bacterial phyla are color coded and labeled in the corresponding colored ring. Taxa reported to be associated with diatoms in culture or field samples are labeled in the outer ring. Boldface genera were reported in two or more independent studies. The tree is based on a concatenated alignment of 31 conserved predicted proteins from 350 bacterial species with whole genome sequences (188). Asterisks indicate taxonomic positions that are estimated from nearest 16S neighbor on the tree because they were not included in the original alignment. *Rhodovulum* nearest 16S neighbor, *Rhodobacter* (164); *Ruegeria* nearest 16S neighbor, *Silicibacter* (190); *Stappia* nearest 16S neighbor, *Xanthobacter* (105); *Limnobacter* nearest 16S neighbors, *Burkholderia* and *Cupriavidus* (111); *Neptunomonas* nearest 16S neighbor, *Marinomonas* (192); *Halomonas* nearest 16S neighbor, *Chromohalobacter* (6); *Alteromonas* and *Glaciecola* nearest 16S neighbor, *Pseudoalteromonas* (85); *Sulfitobacter* and *Staleya* nearest 16S neighbor, *Roseobacter* (106); *Croceibacter*, *Aequorivita*, and *Lacinutrix* nearest 16S neighbor, *Flavobacterium* (10); *Reichenbachia* and *Gelidibacter* nearest 16S neighbor, *Cytophaga* (112, 175); *Winogradskyella* nearest 16S neighbor, *Gramella* (108); *Maribacter* nearest 16S neighbor, *Bacteroides* (10); *Richelia* and *Calothrix* nearest 16S neighbor, *Nostoc* (97a). Abbreviations: β-proteo, *Betaproteobacteria*; δ-proteo, *Deltaproteobacteria*; Ac, *Acidobacteria*; ε-proteo, *Epsilonproteobacteria*; A, *Aquificae*; Bacteroid, *Bacteroidetes*; C, *Chlorobi*; C/V, *Chlamydiae* and *Verrucomicrobia*; P, *Planctomycetes*; S, *Spirochaetes*; Cyano, *Cyanobacteria*; Ch, *Chloroflexi*; F, *Fusobacteria*; Sy, *Synergistetes*; T, *Thermotogae*; and D, *Deinococcus-Thermus*. (Tree modified from reference 174 by permission of Macmillan Publishers Ltd.)

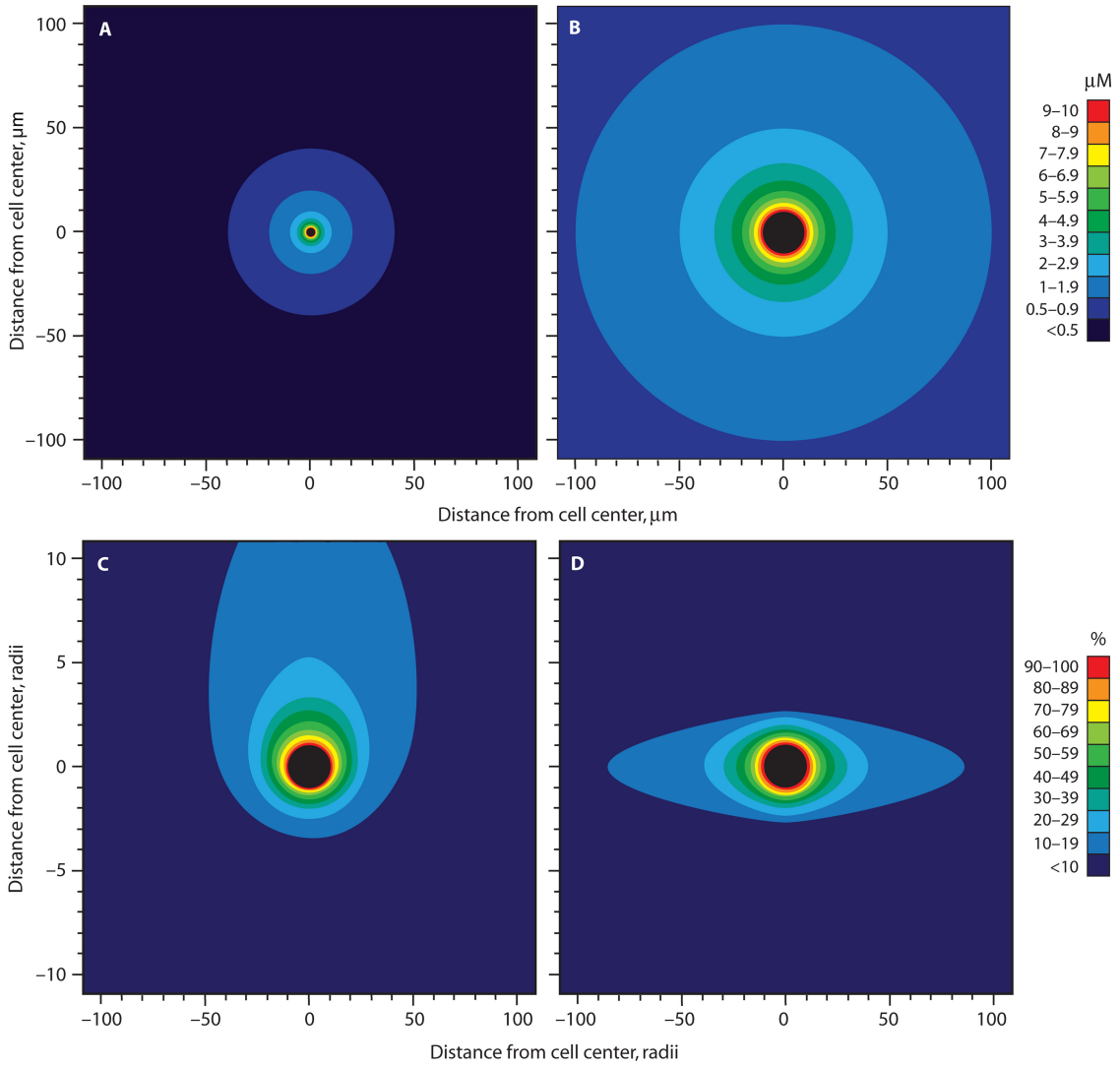

FIG 3 Diffusive boundary layer around a spherical diatom cell (black circle) under different flow scenarios. (A and B) Stationary cell (pure diffusion) with a 4-μm diameter (A) or with a 20-μm diameter (B); (C) sinking cell in the absence of flow; (D) cell in shear flow. Panels A and B demonstrate the effect of cell size on the concentration gradients of a compound excreted from the cell surface and consequently on the size of the diffusive boundary layer. Panels C and D show the effect of sinking or swimming and shear flow on the shape of the diffusive boundary layer of a spherical cell. Panel D shows compression of the boundary layer in the *y* and *z* directions (with *z* being into the page) and stretch in the *x* direction in response to a uniaxial flow. Axes represent the distance away from the cell center either in μm (A and B) or in cell radii (C and D), and contours represent concentration ranges in μM (A and B) or in percentage of surface concentration (C and D). Panels A and B were calculated using equations 1 and 2 for cell surface and bulk (seawater) concentrations of 10 μM and 0.01 μM, respectively. Panels C and D are based on data from reference 95.

the reliance of *Medicago truncatula* (alfalfa) on the nitrogen-fixing bacterium *Sinorhizobium meliloti*. In this system, the plant excretes flavonoid molecules that stimulate the bacteria to produce an oligopolysaccharide known as the Nod factor (61), which in turn induces plant root cortical cell division and curling of the root hairs to incorporate or "trap" a symbiotic bacterial colony and is thus vital to initiating the symbiosis (87).

Diatoms release extracellular organic biomolecules, often called transparent exopolymer particles (TEP), either actively or as a product of cell lysis (58, 136). These mostly particulate acidic polysaccharides are abundant in the ocean and are often colonized by bacteria (136). Analogous to flavonoid production by plants, active diatoms may use TEP to attract certain types of bacteria. The bacteria would recognize the presence of the diatom and initiate attachment to TEP, which may also act as a nutrient source for bacteria. Several strains of bacteria have been found to influence TEP production when added to bacterium-free cells of the diatom *Thalassiosira weissflogii*. These bacteria attach to the diatom and subsequently induce diatom cell aggregation. The mechanism appears to be highly dependent on the identity of the bacteria (62).

Bacteria also release exopolysaccharides (EPS) in response to the presence of phytoplankton, likely to initiate attachment. Rinta-Kanto et al. found evidence for this mechanism using next-generation sequencing (NGS) technology to examine the transcriptional response of heterotrophic bacteria to an induced diatom-dominated bloom in a microcosm compared to that of a nonbloom control. The authors observed significantly more

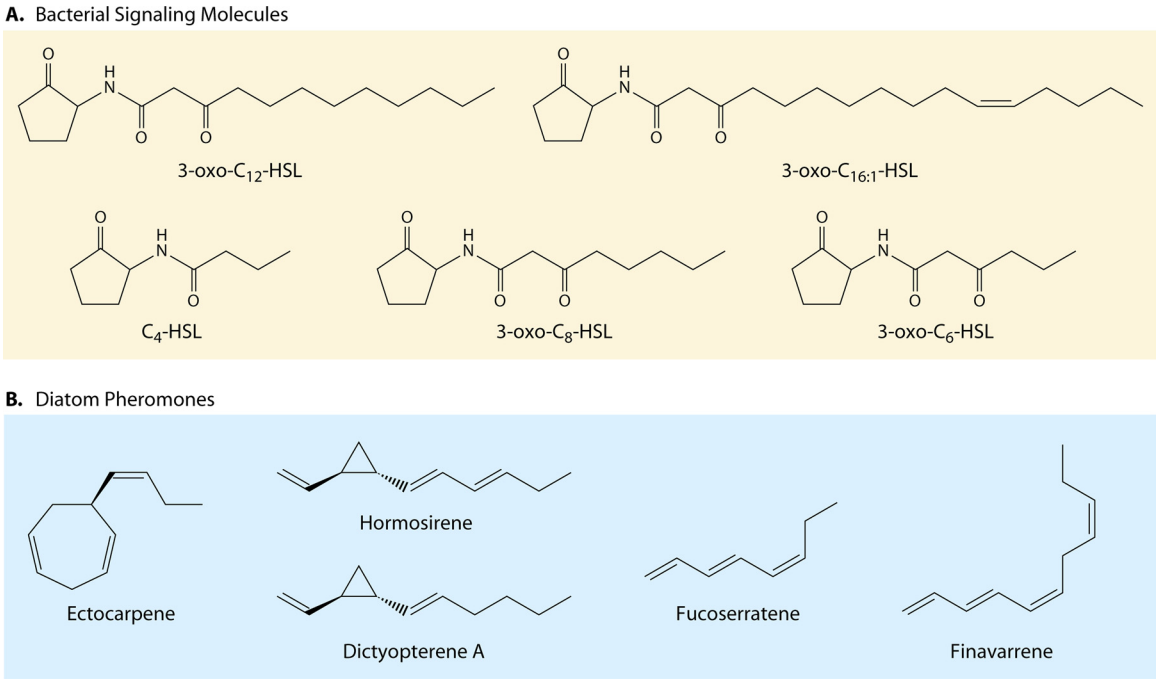

FIG 4 Structures of hydrophobic signaling molecules produced by diatoms and bacteria. (A) Examples of quorum-sensing autoinducers produced by bacteria shown to have a role in interkingdom signaling: 3-oxo-C_{12}-HSL and C_4-HSL (*Pseudomonas aeruginosa*), 3-oxo-C_{12}-HSL (*Vibrio fischeri*), 3-oxo-C_8-HSL (*Agrobacterium tumefaciens*), and 3-oxo-$C_{16:1}$-HSL (*Sinorhizobium meliloti*). (B) Pheromones produced by diatoms.

abundant bacterial transcripts in the bloom than in the control, which corresponded to genes involved in dissolved organic matter (DOM) and organic acid uptake as well as cell surface adhesion, such as EPS production (146). These results suggest that DOM and organic acids may have been released by the phytoplankton during the bloom and that the increase in bacterial EPS production may mediate microbial aggregate formation and cell-cell attachment (146).

The ability of bacteria to attach to TEP and the possibility that the bacteria themselves release extracellular components that allow attachment to the diatom cell wall are important venues for future research. In particular, exploration into the genetic and molecular targets of elements involved in diatom-bacterium encounters within the phycosphere will help to elucidate the biogeochemical significance of these interactions. How motility/attachment and subsequent interactions are established likely involves initiation through signaling and recognition of interaction partners.

DIATOM-BACTERIUM COMMUNICATION

Signaling between diatoms and bacteria is likely a precursor for specific interactions and could allow diatoms to "nurture" specific bacteria in their phycosphere or to facilitate bacterial attachment to diatoms. Interkingdom signaling within the marine environment is a new field. The vast majority of current data concerns intra- and interspecies communication within bacteria and to a lesser extent in diatoms. Interkingdom signaling in terrestrial systems has been shown to initiate and regulate interactions between species and likely plays the same role in the oceans. Below we discuss how bacteria communicate with each other, how diatom cells communicate among themselves, and how both systems and their signaling molecules may overlap to allow diatom-bacterium signaling.

Quorum Sensing in Bacteria

Quorum sensing (QS) is a bacterial cell-cell communication that relies on the biosynthesis and excretion of small molecules, called autoinducers, to synchronize cell population density and gene expression. This process allows bacterial populations to switch gene expression patterns between two modes: low-cell density and high-cell density scenarios. The ability to switch between these two programs allows cells to respond individually or collectively to changes in their environment. The first QS system was discovered in the bioluminescent marine bacterium *Vibrio fischeri*, which colonizes the light organ of its symbiont squid, *Euprymna scolopes* (126). In this system, the luciferase enzymatic activity needed to catalyze bioluminescence occurs only at high bacterial cell density, as luminescence of a small number of cells would be inefficient. QS systems share a two-component architecture (synthase/response regulator). Many Gram-negative bacteria possess the LuxI/LuxR two-component system that was first characterized in *V. fischeri*. Low-molecular-weight QS compounds, or autoinducers (AIs), are synthesized via an AI synthase (e.g., LuxI) and secreted outside the cell. As cell numbers in a population increase, so does the concentration of the secreted AIs. Once the concentration of AIs reaches a threshold required for detection, they bind specific response regulators (e.g., LuxR), causing a conformational change and triggering a signal transduction cascade that results in the regulation of multiple genes (127).

The major class of AIs produced by Gram-negative bacteria is the acyl homoserine lactones (AHLs). These compounds are generally composed of an acyl chain varying from C_4 to C_{18} in length

attached to a lactone ring, sometimes with other minor modifications (Fig. 4A). Because of their hydrophobicity, AHLs passively diffuse through the cell membrane, and their cognate receptors are located within the cytoplasm.

Many bacteria in the ocean possess AI synthases and response regulators as evidenced from genomic and environmental sequence databases (33). In addition, many marine bacteria, including *Vibrio* spp., have been shown to produce AIs (mostly AHLs) in laboratory cultures (reference 47 and references therein). AHLs have been detected in various environments, including subtidal biofilms, where they affect larval settlement, and also microbial mats, where a variety of AHLs were detected (40, 79). Recently, Van Mooy et al. detected AHLs from colonies of the cyanobacterium *Trichodesmium* from the North Pacific that contain diverse bacteria (176). Particulate organic carbon (POC) collected offshore from Vancouver Island also contained AHLs. Exogenous addition of AHLs to bottle incubations containing sinking POC increased the activity of bacterial hydrolytic enzymes involved in POC degradation, potentially linking the production of these enzymes and quorum sensing (75). These studies suggest that AHLs are important in regulating gene expression in the marine environment.

Diatom Cell-to-Cell Signaling

Eukaryotes are also known to utilize QS. Many fungal species secrete AIs and regulate their gene expression accordingly (77). Social insects also use QS to coordinate colony functions such as nesting site selection (141). Although knowledge of the mechanisms underlying diatom cell signaling lags significantly behind knowledge of those of bacteria, there are a number of areas of potential promise.

Pheromones are defined as compounds that coordinate activities between individuals of the same species (93), and they share characteristics with the quorum-sensing mechanism. Most pheromones, like QS AHLs, are lipid-based hydrophobic molecules that can cross the cell membrane without the need for cell surface receptors and presumably coordinate gene expression between gametes. Pheromone-based attraction between gametes of the opposite sex has been known for some time for brown macroalgae (e.g., *Fucus* and *Ectocarpus*), which are related to diatoms, both belonging to the Heterokontophyta (140). Freshwater and marine diatoms were observed to produce C_8 and C_{11} hydrocarbons that were classified as pheromones based on attraction of gametes to the purified compounds. Examples include homoserine, dictyopterine A, and finavarrene, which are produced by *Gomphonema parvulum* (139), fucoserratene, which is produced by *Asterionella formosa* (78), and ectocarpene, which is produced by *Skeletonema* (Fig. 3B) (43). Like many diatoms, *Pseudostaurosira* produces motile male gametes. When male and female clones were separated by solid agar, they initiated sexual reproduction, suggesting involvement of a diffusible pheromone. Subsequent experiments with female filtrates added to male vegetative cells induced gamete release; sexualized male-cell filtrates induced sexualization in female cells, suggesting that both females and males produce a pheromone (156). This study provides strong evidence that diatoms secrete signaling molecules that influence different aspects of the life cycle.

Two additional signaling mechanisms have been discovered in diatoms. Nitric oxide (NO) has been hypothesized to function as an infochemical in diatoms, similar to what has been observed in plants (42). Elevated intercellular NO levels are thought to act as a signaling mechanism to nearby cells to immunize them against stress conditions. Vardi et al. demonstrate the activation of NO production by the diatom-derived reactive aldehyde (2*E*,4*E*/*Z*)-decadienal (DD) and subsequent propagation of the NO signal to neighboring cells (178). Production of DD and other polyunsaturated aldehydes (PUA) by diatoms has been implicated as a chemical defense against grazers (83, 110, 186). The two enzymes primarily responsible for PUA production are phospholipase A2 and lipoxygenase (LOX) (140). LOXs have been shown to catalyze the production of pheromones, some of which have been proposed to have a dual role in defense against grazers and as a gamete attractant. Future work is needed to better understand the roles of different signals secreted by diatoms and their importance in cell-cell communication. Directed-metabolite studies may identify additional molecules and uncover their biosynthetic pathways.

Interkingdom Signaling

The ability of many marine bacteria to secrete autoinducers and of diatoms to synthesize and secrete molecules such as pheromones with similar functionality suggests that these types of compounds could function as two-way signals between diatoms and bacteria. This process, also known as interkingdom signaling, has been documented widely in terrestrial environments, particularly in mammal-pathogen systems and in rhizobia (80, 151). A common feature of many bacterial and diatom signals is that they are lipid-based molecules that have relatively poor solubility in aqueous solutions (Fig. 4A and B), which means that active transport across membranes, an energy-demanding process, is not required. Hydrophobicity also limits diffusion and loss of these molecules to bulk seawater.

The ability of a diatom cell to sense bacterial species' signals within its phycosphere would confer a fitness advantage over a nonsensing cell unable to detect bacteria, particularly algicidal bacteria. Hydrophobic molecules (e.g., AHLs) may be prime targets for the diatom to sense, since they could accumulate inside a diatom cell, as they do inside plants and mammals (27, 179), without the need of cell surface receptors. Likewise, bacterial species that are able to sense a diatom signal would have a competitive advantage over bacteria that use only traditional chemotaxis to sense transient nutrient patches. A pheromone produced by a diatom can enter a bacterial cell and trigger a response. Consequently, it is possible to interpret consistent associations between certain species of bacteria and diatoms as the ability to sense a shared signal. This section provides examples of interkingdom signaling, with drawn conclusions that are applicable to diatoms and associated bacteria.

Eukaryotes sense bacteria. The majority of research on interkingdom signaling in the terrestrial world focuses on the effects of bacterial quorum-sensing molecules, and in particular AHLs, on eukaryotes. For example, when plants are exposed to the QS signal 3-oxo-C_{12}-homoserine lactone (3-oxo-C_{12}-HSL) from the pathogen *Pseudomonas aeruginosa* or to 3-oxo-$C_{16:1}$-HSL (Fig. 4A) from the plant symbiont *S. meliloti*, more than 60 plant proteins are similarly differentially expressed and accumulate in the roots. These proteins may represent a general response to bacterial AHLs. Thirty additional proteins show differing responses to the two AHLs, in either magnitude or direction of accumulation (119), suggesting that these proteins respond to specific AHLs and that *M. truncatula* distinguishes between pathogenic and symbi-

ont bacteria based on the identity of the bacterial AHL. Humans also sense AHLs (e.g., 3-oxo-C_{12}-HSL) from *P. aeruginosa* (161) and attempt to fend off the bacterium by degrading its AHL via activation of the lactonase activity of the paraoxonase (PON-2) enzyme (133, 169).

In the phycosphere, two different bacteria consistently associated with a diatom may produce different hydrophobic AHL molecules that passively enter and accumulate inside the diatom cell. Once inside the cell, these molecules may bind to different molecular targets and initiate different responses that reflect whether these bacteria are synergistic or algicidal. Crystal structures of many bacterial AHLs and their respective regulators display close three-dimensional (3D) homology to PAS and GAF domains (23, 177), which are conserved in both bacterial and eukaryotic proteins (76). Eight and four gene models in the genomes of the diatoms *Thalassiosira pseudonana* and *Phaeodactylum tricornutum*, respectively, appear to have GAF domains (M. S. Parker, unpublished results), suggesting that some of these may respond or bind to AHLs. Further research on the diatom response to AHLs and the molecular targets of these signals is needed.

Bacteria sense eukaryotes. Bacteria detect and respond to signals from eukaryotes. For example, *E. coli* produces the iron siderophore enterobactin after detecting the mammalian stress hormones epinephrine and norepinephrine (28). The response to the two hormones is mediated through the *E. coli* sensor kinase QseC, suggesting that QseC has evolved to respond to host signals (37). The acquisition of the ability to sense epinephrine and norepinephrine is thought to allow pathogens to gauge and thus exploit the host during metabolic stress. This conclusion has been corroborated by the ubiquity of QseC homologs in other pathogens, such as *Salmonella enterica* serovar Typhimurium and *Vibrio parahaemolyticus* (80). *V. fischeri* colonizes the light organ of the bobtail squid following the squid's secretion of the signal nitric oxide (NO). NO is perceived by the bacterial *hnox* gene, which encodes a heme NO/O_2-binding protein. This protein, in addition to sensing host-generated NO, affects utilization of iron in the iron-limited light organ of the squid during early stages of infection (183).

The ability of bacteria to sense animal and plant compounds suggests that marine bacteria associated with diatoms should be able to sense excreted pheromones or signaling molecules. If these molecules can act as targets for a bacterium to sense a diatom, then pheromones, as well as other diatom signals, may serve a dual role. For example, under stress conditions, the NO released by diatoms into the phycosphere may attract NO-sensing scavenger bacteria that attack these stressed or dying cells; under nonstress conditions, released NO may act as a signal to synergistic bacteria and an antimicrobial agent to bacteria that cannot detoxify it (41).

Signaling may be as important to diatom-bacterium interactions as it is essential for interspecies signaling in the terrestrial environment. Identifying signals and their molecular targets will lead to better characterization of diatom-bacterium interactions.

DIATOM-BACTERIUM INTERACTIONS

The consistent presence of specific species of bacteria in diatom cultures and with diatom communities from field studies suggests that these bacteria are adapted to utilizing products from diatom cells. Diatoms seem able to "cultivate" their phycosphere by releasing organic-rich substances utilized by some bacteria. This cultivation may entail diatoms secreting pheromones that are perceived by the bacteria; perception of the pheromones may then lead to rapid activation of acquisition genes for diatom-specific products before they diffuse away. Signaling then ensures that only specific bacteria, those able to perceive diatom signals, form consistent associations and engage in specific interactions with diatoms. Bacteria may benefit diatoms by providing more available sources of nutrients or by protecting the diatoms as they deter other opportunistic bacteria. On the other hand, a subset of these associated bacteria may be able to exploit diatoms by causing stress or cell lysis. These concepts strongly support the existence of specific interactions between diatoms and their bacterial counterparts. Below we discuss well-studied examples of diatom-bacterium interactions where a chemical or a mechanism has been elucidated.

Synergistic Interactions

Vitamins. A commonly investigated interaction between bacteria and diatoms (and phytoplankton in general) is bacterial production of vitamins required by different diatom species. Early studies suggested a strong correlation between vitamin depletion in seawater and diatom bloom termination (129, 130). Cobalamin, or vitamin B_{12}, is by far the most studied vitamin in relation to diatom requirements (32, 50, 152). Cobalamin is required in organisms lacking the cobalamin-independent methionine synthase, MetE. The most prominent study of potential interactions involving B_{12} was conducted in 1974, when several diatom species were grown axenically in the presence or absence of B_{12} and in the presence of heterotrophic, B_{12}-producing marine bacteria. In almost all cases the bacteria seemed to improve diatom cell yield relative to that in the B_{12}-limited cultures but never to the level of the B_{12}-supplemented cultures (70). More recently, Croft et al. conducted a literature survey of vitamin B_{12} requirements in 326 algal species and confirmed this requirement in select cases (39). The presumed B_{12} auxotrophy did not mirror algal lineages, suggesting multiple gains and losses of some of the 30 enzymes required for the biosynthesis of B_{12}. They found that about 52% of the surveyed heterokonts were not able to grow in B_{12}-deficient medium, indicating the importance of the vitamin to diatoms (39). They also demonstrated that a bacterium from the genus *Halomonas* increased production of B_{12} when provided with fucoidin, a commercial algal extract, which they interpreted as evidence that bacteria supply vitamins (and particularly vitamin B_{12}) on a global scale to most B_{12}-auxotrophic phytoplankton in exchange for fixed carbon (this scenario is depicted in Fig. 5). The observed interaction may also have been due to a general increased growth and fitness of the bacterium in response to the algal exudate rather than to a specific synergistic interaction. Droop later hypothesized that the extremely low requirements for cobalamin of many algal species could be fulfilled by scavenging rather than by a required synergism (51).

More recent work indicates that 60% of examined heterokonts (49 of 82 species) require B_{12} and that a small proportion (15 and 7%, respectively) require B_1 and B_7 (171). Each of these vitamins is biosynthesized by bacteria and, given microscale patchiness (21), may serve as part of a synergistic interaction. In addition, marine archaea have been found to contain cobalamin biosynthesis machinery, and with a strong correlation in the sediment record between phytoplankton and archaea, it is possible that archaea may also provide this vitamin to diatoms (55, 148). All three vitamins are water soluble, and diatoms must rapidly assimilate them before they diffuse outside the phycosphere.

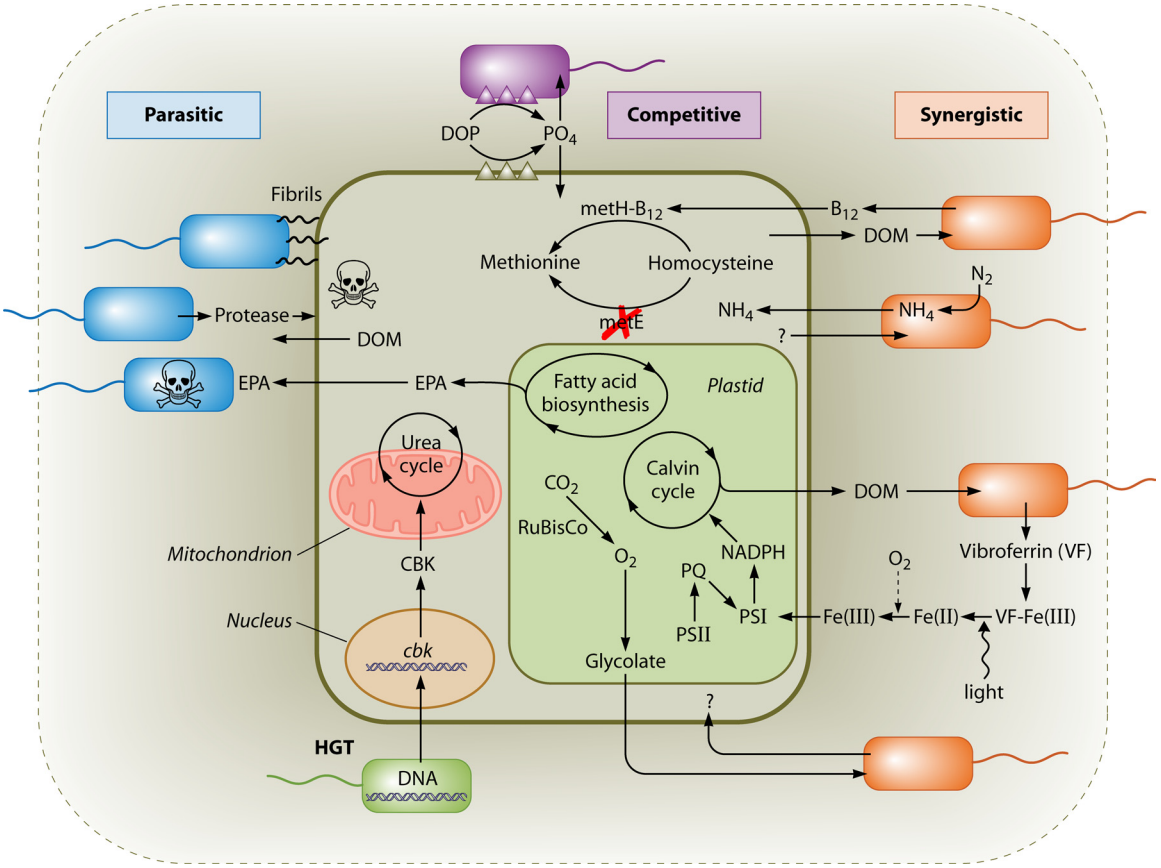

FIG 5 Depictions of microbial interactions. Examples of bacterial interactions with diatoms are shown, categorized as competitive (purple), synergistic (orange), and parasitic (blue). An example of horizontal gene transfer (HGT) as evidence for past associations between diatoms and bacteria is also shown (green). Small rectangles with flagella represent bacteria; the large dark green rectangle (center) represents a diatom cell. Key reactions involved in the interactions are depicted within respective cells. The background gradient and dashed line represent the phycosphere. In the nutrient-poor regions of the oceans, bacteria and diatoms often encounter limiting resources for which competition may be established. Bacteria and diatoms both produce membrane-bound enzymes, such as alkaline phosphatase and 5′-nucleotidases (triangles), to break down dissolved organic phosphorus (DOP). Unless coupled directly to an uptake mechanism, consequent release of orthophosphate into the surrounding seawater may result in competitive uptake by both organisms, with bacteria generally outcompeting diatoms at low concentrations (173). One way to avoid such competition is to establish a synergistic mutualism, in which an exchange of resources increases the fitness of both organisms. For example, some diatoms lack a B_{12}-independent methionine synthase gene (*metE*) and thus require an exogenous source of vitamin B_{12} to synthesize methionine. Many bacteria can produce B_{12}, thus providing a source for diatoms (70). In return, the bacteria would benefit from dissolved organic matter (DOM) produced by the diatoms. Nitrogen-fixing cyanobacteria have been shown to supply fixed nitrogen to diatoms, likely in the form of ammonia or dissolved organic nitrogen (57). Some bacteria produce the highly photolabile siderophore vibrioferrin, which has been shown recently to supply soluble iron to algal cells, presumably in exchange for DOM (4). In this case, bacterial growth is significantly enhanced in the presence of the algae, providing further evidence for a mutualistic interaction. A subset of bacteria possesses the ability to utilize a by-product of algal photorespiration, glycolate, with the potential consequence of shifting bacterial community dynamics over diel cycles (101). In the category of parasitic interactions, we include interactions that directly parasitize or defend against such parasitism. Desbois et al. have shown that the fatty acid eicosapentaenoic acid (EPA) produced by the diatom *P. tricornutum* is an effective antimicrobial agent against known human pathogens (45). The compound appears to be less effective against marine bacteria. Algicidal bacteria can attack diatoms through attachment and/or release of enzymes that degrade the diatom's organic matrix, which protects the silica frustule from dissolution. Furusawa et al. demonstrated the attachment of a *Saprospira* sp. to a diatom and subsequent release of fibril-like materials that appear to aid in decomposition of the cell wall (60). The algicidal bacterium *Kordia algicida* appears to produce a diffusible protease responsible for the killing activity (137). In a similar system, Lee et al. characterized the protease from a *Pseudoalteromonas* sp. as a serine protease (107). Horizontal gene transfer (HGT) represents the footprint of ancient associations between bacteria and diatoms. Horizontal transfer of genetic material, hypothesized to originate from bacteria in close associations with diatoms, has shaped the metabolic potential of modern diatom species. In one example, a key offshoot pathway of the urea cycle in diatoms, catalyzed by carbamate kinase (CBK), appears to be encoded by a gene with no phylogenetic associations with other known eukaryotes (2).

Sensing AHLs from vitamin-producing bacteria may allow diatoms to activate vitamin acquisition genes rapidly before vitamin diffusion. Advances in detection of vitamins B_1 and B_{12} in seawater should also spark more interest in examining the importance of these vitamins in diatom-bacterium interactions and aid molecular biology methods to understand vitamin cycling in the oceans (131, 132).

Iron. Iron is a micronutrient required by all life on Earth except a group of *Lactobacillus* bacteria (84). Iron is required at relatively higher concentrations on a per-cell basis than all other transition metals owing to its ability to catalyze redox reactions, transfer electrons, and reversibly bind and thus transport ligands such as dioxygen. In addition, iron availability is hypothesized to have been much higher during the evolution of the first microbes. The scarcity of dissolved iron in the present aerobic marine environment, typically at subnanomolar levels in the open ocean, has

driven microorganisms to adopt multiple strategies to acquire and compete for this essential metal (25).

Many marine bacteria synthesize and excrete small organic compounds, called siderophores, that bind the ferric ion with exceptionally high affinity. An emerging structural feature of marine siderophores is the presence of iron-binding α-hydroxy acid moieties that make the resulting iron complexes photolabile (30). Upon exposure to light, bound Fe(III) is reduced to Fe(II) with the concomitant oxidation and loss of CO_2 from the siderophore via an irreversible internal redox reaction (14). The photogenerated Fe(II) rapidly oxidizes under aerobic oceanic conditions to a soluble form of iron, designated Fe(III)′, that is expected to be bioavailable to microorganisms, especially phytoplankton. Thermodynamic measurements indicated that the oxidized siderophore photoproducts maintain an exceptional affinity for Fe(III), recomplexing it and thus potentially continuing to restrict its bioavailability (1, 98). One stark exception to this paradigm is the siderophore vibrioferrin, which is produced by a number of gammaproteobacteria belonging to the *Vibrio* and *Marinobacter* genera (5, 189). The iron complex of vibrioferrin is more photosensitive than all previously examined siderophores, with a half-life in attenuated sunlight of <7 min. Since the majority of the *Marinobacter* spp. that produced it were found consistently associated with diverse algal cultures, including diatoms (3), the photochemistry of vibrioferrin was shown to provide a steady supply of soluble Fe(III)′ to algal cells, potentially in exchange for organic carbon (Fig. 5) (4). In addition, the vibrioferrin biosynthesis marker gene *pvsA* has been detected in the North Atlantic, suggesting that this siderophore is ecologically important (S. A. Amin, unpublished data).

Quorum sensing regulates siderophore biosynthesis and excretion in many bacteria (167, 182). To effectively acquire iron from siderophores, a diatom must rapidly respond to the excretion of siderophores within the phycosphere. If diatoms can sense AHLs produced by a siderophore-producing bacterium, they can quickly mobilize iron assimilation mechanisms. Unlike hydrophobic AHLs that readily cross cell membranes, siderophores are hydrophilic and require specific cell surface receptors. Targeted screening of photolabile siderophore production from marine bacteria and QS regulation of these siderophores, especially those belonging to bacteria consistently associated with diatoms, may provide further evidence for iron-based interactions.

Eukaryotic phytoplankton species do not produce siderophores and instead appear to produce other compounds to access the low quantities of iron available in the surface ocean. Many algal species, including diatoms, release significant quantities of monosaccharides and polysaccharides (109, 136) that display a weak binding affinity for iron. High concentrations of saccharides (especially cell-associated polysaccharides) are expected to accumulate within the phycosphere. A recent study found that the addition of saccharides enhanced iron bioavailability to phytoplankton assemblages in the Southern Ocean. Similar experiments were conducted on an axenic diatom isolate of a *Chaetoceros* sp., which demonstrated similar results (73). Do saccharides that accumulate within the phycosphere help create iron (and carbon) pools available to some bacteria? Support for this hypothesis comes from the observations that bacteria can attach to algal polysaccharides (117) and that many bacteria do not produce their own siderophores and instead access iron from siderophores produced by other bacteria (49).

Several species of the genus *Pseudo-nitzschia* produce the small molecule domoic acid (DA), which acts as a neurotoxin in vertebrates (71) and also binds iron and copper. DA has been hypothesized to play a role in acquisition of both metals (150), and production of DA appears to increase when *Pseudo-nitzschia* cells are Fe limited or Cu stressed (with a low or high copper concentration) (114, 184). The affinity of DA for iron and copper is relatively weak. Since DA binds copper with a higher affinity than iron and copper is generally more abundant than iron in seawater, it is unlikely that DA binds iron except under unusual circumstances. Some diatoms assimilate iron by reduction of Fe(III) bound to organic ligands to Fe(II) via a cell surface ferric reductase followed by oxidation of the iron back to Fe(III) via a multicopper oxidase (MCO) (99, 113). The synergy between iron, copper, and DA led to the hypothesis that DA supplies copper to *Pseudo-nitzschia* cells, which ultimately incorporate it in their MCO as part of their high-affinity iron uptake system (184). It remains to be demonstrated whether DA is part of a complex copper-iron uptake system in *Pseudo-nitzschia* and whether the primary role of DA is as a metal chelator. Another level of complexity for the exact role of DA is added when one considers the effect of bacteria on DA production. It has been widely reported that bacteria influence the rate of biosynthesis of DA, with axenic cultures producing very low levels of the neurotoxin (15, 16, 96, 165, 166). The recent finding that the bacterial community composition differs between DA-producing and non-DA-producing *Pseudo-nitzschia* spp. may be related to DA and, if so, suggests that DA may act as a bacterial deterrent against unwanted or algicidal bacteria and/or, conversely, may encourage the growth of favorable bacteria (66). To better understand the interplay between bacteria and DA biosynthesis, the effect of DA on bacterial diversity needs to be investigated, especially given recent evidence that some bacteria may be able to degrade DA (69). In addition, the biosynthetic pathway of DA has not yet been determined, though theoretical biosynthesis pathways have been proposed based on stable isotope uptake experiments (143). The identification of the biosynthetic pathway will undoubtedly reveal more about the role of this enigmatic toxin.

Dissolved organic carbon (DOC). Perhaps some of the most important substrates provided by autotrophic diatoms to heterotrophic bacteria are dissolved organic carbon (DOC) compounds. The paradigm in the marine environment is that autotrophs fix carbon and heterotrophic bacteria assimilate and decompose a significant proportion of this carbon (36). The variety of DOC produced by diatoms likely plays a role in shaping the diversity of associated bacteria. For example, EPS polymers produced by diatoms have been implicated in promoting growth of specific bacterial taxa in estuarine biofilms (74). Glycolate is a small 2-carbon, water-soluble molecule produced by photoautotrophs as a byproduct of photorespiration and also appears to shape bacterial community structure. Specific subsets of bacteria possess the glycolate utilization gene *glcD*, which suggests that only some bacterial species would benefit from associating with glycolate-releasing diatoms and other phytoplankton (100). Sensing diatom signaling molecules that accumulate in the phycosphere may enhance the ability of diatom-associated bacteria to assimilate glycolate before it diffuses away or is consumed by competing *glcD*-containing bacteria. Follow-up studies during a phytoplankton spring bloom showed that mRNA transcripts of *glcD* varied over the diel cycle, with a consistent increase in transcripts during the

day (Fig. 5) (101) when glycolate production is at a peak (104), suggesting that these bacteria have coupled their metabolism to glycolate availability. Interestingly, the diversity of *glcD* sequences varied as the bloom progressed, suggesting complex dynamics within the bacterial population as a result of competition for glycolate (101). This last observation perhaps best illustrates how algal exudates can serve as a selective force to shape bacterial communities.

Nitrogen. Nitrogen-fixing microbes in the marine environment play a pivotal role in the nitrogen cycle by converting dinitrogen gas into biologically more available forms such as ammonia. Nitrogen-fixing cyanobacterial filaments contain vegetative cells that specialize in photosynthesis and heterocysts that only fix nitrogen. Cell differentiation and compartmentalization are aimed at avoiding inhibition of the N_2-fixing enzyme nitrogenase by oxygen generated from photosynthesis in vegetative cells. Several examples of symbioses between diatoms, e.g., *Rhizosolenia*, *Chaetoceros*, and *Hemiaulus*, and cyanobacterial diazotrophs, e.g., *Richelia* and *Calothrix*, have been documented. Foster et al. measured rates of nitrogen fixation by cyanobacteria and transport to diatoms using a combination of stable nitrogen isotopes and secondary ion mass spectrometry (NanoSIMS) (57). NanoSIMS relies on emitting a primary ion beam (Cs^+ or O^-) to scan a biological sample releasing secondary ions that can be detected and quantified within a single cell using high-resolution mass spectrometry. The authors reported that the N_2-fixing *Richelia* and *Calothrix* strains fix nitrogen at a 171- to 420-times-higher level when grown with the diatoms than when grown alone. The authors suggest that cyanobacteria fix excess nitrogen and that the majority of the fixed nitrogen is transferred to their symbiont (Fig. 5) (57). The observation of excessive enzymatic activity by heterocysts reinforces the notion of a synergistic interaction with diatoms.

NanoSIMS can also measure the cellular distribution of other nutrients such as copper or iron (31, 162) and can reveal the ability of microbes to take up specific, labeled organic molecules (e.g., algal exudates) (124). Applying this technique to known diatom-bacterium interactions will provide valuable information on the flux of nutrients from one organism to another and the net production by these organisms in the ecosystem.

Other interactions. Some bacteria protect diatoms by detoxifying by-products generated during diatom metabolism. For example, epiphytic bacteria on the Antarctic diatom *Amphiprora kufferathii* relieve the diatom from oxidative stress induced by hydrogen peroxide production that occurs as diatom growth nears stationary phase. Hydrogen peroxide yields highly reactive hydroxide radicals that can inhibit CO_2 fixation. The epiphytic bacterial genomes encode catalases that react with hydrogen peroxide and reduce its accumulation within the phycosphere (81).

Parasitic Interactions and Defense

Bacterial algicidal activities. Interactions between diatoms and bacteria do not always have beneficial consequences; rather, the end result may be the death of one or both partners. Algicidal bacteria attract attention because of their potential application as biocontrol agents of harmful algal blooms (97, 120). A subset of algicidal bacteria are able to enter the phycosphere and release sufficient molecules to kill the diatoms. Quorum-sensing signals, such as AHLs, could potentially regulate the biosynthesis and secretion of these algicides. The flavobacterium *Kordia algicida* releases a protease with a mass of >30 kDa that acts against a subset of diatoms (*Skeletonema*, *Thalassiosira*, and *Phaeodactylum*, but not *Chaetoceros*), indicating taxon-dependent activity. The secretion of the protease occurs only when the bacterial cell density reaches a threshold, suggesting that QS regulates the algicidal activity (137) (protease algicidal activities are depicted in Fig. 5).

Other algicidal bacteria directly attach to the diatom cell to lyse them. The marine isolate *Saprospira* sp. strain SS98-5 lyses cells of the diatom *Chaetoceros ceratosporum* by direct contact. The bacterium uses gliding motility to swim toward the diatom and induces diatom cell aggregation, followed by lysis via production of microtubule-like structures as shown by transmission electron micrographs (depicted in Fig. 5) (60). Further experiments demonstrated that the extracellular structure is a cytoplasmic fibril protein with sequence homology to tail sheath protein domains of bacteriophages (59). Open reading frames (ORFs) adjacent to the gene encoding this fibril protein contain several genes with homology to genes for peptidases and phage-related proteins, indicating a possible role in algicidal activity and a probable phage origin of these genes (191).

Diatom antibacterial compounds. Many diatoms, in turn, have defense mechanisms to protect against unwanted and/or algicidal bacteria. Diatoms secrete fatty acids and esters that can act as antibacterial compounds and influence the bacterial community structure (103). These poorly soluble, hydrophobic molecules would not diffuse far from the diatom cell wall and are expected to readily cross bacterial cell membranes without the need of receptors. Release of these compounds at the cell surface may serve to prevent attachment of unwanted and/or algicidal bacteria.

The diatom *Navicula delognei* produces several antibacterial compounds. Three compounds, the fatty acids hexadecatetraenoic acid and octadecatetraenoic acid and the ester (*E*)-phytol, display strong antibacterial activity against the pathogens *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Proteus vulgaris*, and *Salmonella enterica* serovar Typhimurium (56). *Navicula delognei*, along with the diatom *Phaeodactylum tricornutum*, produces the fatty acid hexadecatrienoic acid (HTA), which is toxic to the marine pathogen *Listonella anguillarum* (44, 56). *P. tricornutum* also produces the fatty acids palmitoleic acid and eicosapentaenoic acid (EPA), both of which inhibit growth of Gram-positive bacteria (44). EPA also weakly inhibits growth of a number of marine bacteria (45) (this interaction is depicted in Fig. 5). Different morphotypes of *P. tricornutum*, oval cells and fusiforms, produce different amounts of antibacterial compounds. Oval cells produce small amounts of fatty acids, are motile, have siliceous valves, and produce EPS, features that may protect them from some bacteria. In contrast, the fusiform morphotype produces copious amounts of fatty acids, is nonmotile, lacks siliceous valves, and does not produce EPS. Desbois et al. hypothesize that fusiforms invest energy into the production of these antibacterial compounds because they lack the defensive features of the oval morphotype (46).

Some fatty acids may play an indirect role in diatom defense against bacteria. For example, diatoms rapidly deplete their fatty acid cell content upon disruption by grazers to produce polyunsaturated aldehydes (PUA) (186). PUA are important for algal cell defense against grazers (83) but also display antibacterial activity against some marine bacteria. When tested against 33 marine bacterial strains, PUA suppressed growth of most bacteria. Diatom-associated bacteria, e.g., *Sulfitobacter*, *Paracoccus*, and *Erythrobacter* (Fig. 2), were resistant to PUA (144), suggesting that diatom-

associated bacteria may have evolved resistance to toxic molecules released by diatoms.

Diatom QS interference. Diatoms may have an additional defense mechanism in their arsenal. Similar to many plants and algae, diatoms may be able to disrupt QS of motile algicidal bacteria within the phycosphere to disable the production of algicidal molecules. Some plants produce leaf surface compounds that interfere with AHL-based quorum sensing (92). In response to stress, many plants produce the nonprotein amino acid gamma-aminobutyric acid (GABA), which modulates QS in the plant pathogen *Agrobacterium tumefaciens*, thus lessening virulence (35). The freshwater alga *Chlamydomonas reinhardtii* produces a range of compounds that stimulate QS in *Vibrio harveyi* and *Sinorhizobium meliloti* (172). Exposure of *C. reinhardtii* extracts containing these compounds to a lactonase, an enzyme that degrades the lactone ring of AHLs, inactivates them (142). The inactivation of the algal molecules by lactonases suggests that *C. reinhardtii* produces AHL mimics that share structural features close to bacterial QS signals. The red alga *Delisea pulchra* inhibits expression of QS genes involved in virulence and antibiotic production in various bacteria (115, 116) by the release of halogenated furanones that mimic the structure of AHLs and bind to their receptors (63).

Another defense mechanism against motile algicidal bacteria is to modify QS signals using enzymatic activity. Haloperoxidases can modify AHLs by halogenating the acyl side chain and thus prevent their binding to QS regulators. Vanadium haloperoxidases, a subfamily of haloperoxidases, from the seaweed *Laminaria digitata* can interfere with QS by brominating AHLs (22). Some haloperoxidases may be surface exposed in some marine algae (29), likely to deactivate AHLs upon contact with the cell surface. Searching the three publicly available genomes of diatoms with Interproscan (128) yielded only one candidate putative vanadium haloperoxidase in *Fragilariopsis cylindrus* (protein ID, 249001; E value = 10^{-12}), with the highest 3D homology to V-haloperoxidase from the brown alga *Ascophyllum nodosum* (fold predicted with CPHmodels 3.0 server; M. S. Parker, unpublished results). This candidate haloperoxidase may be an important target for characterizing potential defense mechanisms of diatoms against unwanted bacteria.

Competitive Interactions

Competition among microbes for essential limiting nutrients is a common theme in many ecosystems. In the oceans, phytoplankton growth is often limited by the availability of macronutrients such as nitrogen and phosphorus or of micronutrients such as iron. Bacteria are also often limited by these nutrients, in addition to carbon. For example, under phosphate limitation, the diatom *Cylindrotheca fusiformis* exhibits slower growth and produces more exopolysaccharides than P-replete cultures. When exposed to bacteria, the diatom growth slows further but only at low phosphate concentrations, suggesting that bacteria scavenge phosphate better than the diatom (67). A field study of competition between phytoplankton and bacteria over phosphate, examined through $^{32}PO_4^{3-}$ uptake measurements, showed that bacteria are indeed superior to phytoplankton in assimilation of phosphate, especially at low ambient concentrations (173) (Fig. 5). Nitrogen is another important macronutrient for which competition has been reported among phytoplankton and bacteria. Benthic microalgae limited ammonia-oxidizing bacteria in a microcosm experiment by depleting ammonia in the sediment (147). In contrast, ammonia-oxidizing archaea are predicted to outcompete diatoms for ammonia because the archaeal ammonia-oxidizing enzymes have a higher affinity to ammonia than diatom cells (118). The different outcomes with archaea and bacteria highlight the potential diversity of interactions between diatoms and other microbes.

CONCLUSION

Diatoms and bacteria coexist in the dilute surface ocean and have coevolved to actively engage in complicated interactions that significantly modify each other's behavior and ultimately impact biogeochemical cycles. Our goal in this review was to identify core features that dominate the seemingly infinite array of potential exchanges. We find that a relatively small set of bacterial taxa likely play a majority role in communicating with diatoms. Further, these communications appear to occur via a constrained set of mechanisms that rely predominantly on the accumulation of hydrophobic molecules near the cell surface that can readily pass through cell membranes to activate physiological responses. The shared currency between partners appears to be vitamins, iron and other trace elements, and dissolved carbon and nitrogen compounds. Hydrophobic signaling molecules that tend to accumulate near cell membranes and within the phycosphere may prime a partner to rapidly assimilate these currencies before they diffuse. We focused here on interactions that occur at the level of single cells of diatoms, although the important concept of a diffusive boundary layer surrounding microbes is readily expandable to communication around larger particles and between other microbial partners.

A small subset of the known heterotrophic bacterial diversity appears to have evolved specific associations with diatoms. Members of the *Alpha-*, *Beta-*, and *Gammaproteobacteria* and *Bacteroidetes* are repeatedly found associated with diatoms, with representation by relatively few genera, such as *Roseobacter*, *Sulfitobacter*, and *Flavobacterium*. This limited number of bacterial taxa that have successfully developed interactions with diatoms likely results from a required coevolution of signaling molecules, receptors, and regulatory cascades. For instance, the intricate communication systems that coevolved in rhizobial symbioses result in a narrow selection of plant-associated symbionts. Similarly, the arms race between pathogen (algicidal bacteria) and host (diatoms) requires a constant coevolution in recognition and defense. Current evidence suggests that the hydrophobic AHL molecules and pheromones will serve as good starting places for understanding interkingdom signaling. One of the challenges in studying these interactions is distinguishing the metabolic responses of diatoms and bacteria to signaling from specific downstream interactions. Development of coculturing model systems that utilize representative members of these bacterial genera and the incorporation of metabolomic approaches are needed to identify additional signaling molecules and resulting responses to these molecules.

Marine archaea are abundant microbes throughout the oceans (94) and are also major drivers of marine biogeochemistry (34). As with the bacteria, are there major archaeal taxa that also associate with diatoms? Our knowledge of their specific interactions with diatoms is essentially nonexistent. A strong correlation between phytoplankton and archaeal chemical markers in the sediment record suggests that interactions between the two groups are likely (55). Recent evidence that marine group II euryarchaea are

abundant in surface waters and appear to consume proteins and lipids produced during the spring bloom in the Pacific Northwest again suggests potential interactions between diatoms and archaea (86). Uncovering the types of interactions among diatoms and archaea and their relative influence on ocean biogeochemistry and deciphering the language that establishes communication between these two groups are exciting new areas of research to pursue.

The ocean environment is changing rapidly as the ocean temperature increases and the pH decreases (48). How will these changes impact the elaborate dependencies that appear to occur within microbial communities? Will ocean acidification shift the bioavailability of shared currency such as trace metals (160) and impact these interactions? Will interactions that are currently commensal shift toward competitive interactions, as was observed in an early study of diatom-bacterium cocultures maintained in phosphate-limited chemostats (26)? As noted at the start of this review, marine ecosystems consist of networks of interacting organisms. Understanding the range and resilience of ecosystem interactions and incorporating this information into global models are essential for predicting responses to the external forces associated with a changing climate. Identifying core modes of microbial interdependencies is a crucial starting place.

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Shady A. Amin received his Ph.D. in inorganic chemistry from the University of California at San Diego and San Diego State University. During his doctoral studies, he showed that siderophores produced by alga-associated marine bacteria provide algae with bioavailable iron through a photochemical reaction in exchange for fixed carbon. He also explored boron metabolism in marine microbes. He is currently a postdoctoral scientist in the School of Oceanography at the University of Washington. His current research interests include identifying the molecular basis for diatom-bacterium communication and interactions using environmentally relevant model systems, unraveling copper acquisition mechanisms and metabolism of marine ammonia-oxidizing archaea in the context of competition with diatoms, and investigating diatom-archaeon associations and interactions.

Micaela Parker earned her M.S. and Ph.D. in oceanography from the University of Washington. For her Ph.D. thesis, she used molecular tools to study the metabolic cycling of carbon and nitrogen in diatom cells during photorespiration. Her interest in diatom-microbe interactions began during predoctoral studies in plant pathology at Cornell University, where she worked on both plant responses to and biocontrol agents for bacterial pathogens. Since 2004, she has been a research scientist working with Dr. E. Virginia Armbrust in the School of Oceanography at the University of Washington. She uses comparative functional and evolutionary genomics and transcriptomics to better understand the underlying molecular basis for diatom success in the marine environment. She has taken part in many algal genome projects in collaboration with the Joint Genome Institute, including coleading the current *Pseudo-nitzschia multiseries* genome project. Her current interests include examining the extent to which microbial interactions shape diatom genomes, physiology, and metabolism.

E. Virginia Armbrust is a Professor of Oceanography at the University of Washington in Seattle, WA. She received her Ph.D. from the Massachusetts Institute of Technology and the Woods Hole Oceanographic Institution, where she first began working with marine diatoms. She conducted postdoctoral research at Washington University, where she studied the molecular genetics of chloroplast inheritance in green algae. Since her arrival at the University of Washington in 1996, she has focused on understanding the roles of diatoms in marine ecosystems. Her work combines genomics and physiological approaches to address questions that span a range of spatial and temporal scales. Current areas of interest include the basis of molecular interactions between diatoms and other microbes, the factors that control the abundance and distribution of marine algae across ocean basins, and the impact of past and future conditions on the distributions and interactions of diatoms in the sea.