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Review Article

REVIEW ARTICLE

Strategies and ecological roles of algicidal bacteria

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One sentence summary: This review summarises current knowledge on the interaction of algicidal bacteria and microalgae with special emphasis on ecological and functional aspects.
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ABSTRACT

In both freshwater and marine ecosystems, phytoplankton are the most dominant primary producers, contributing substantially to aquatic food webs. Algicidal bacteria that can associate to microalgae from the phytoplankton have the capability to control the proliferation and even to lyse them. These bacteria thus play an important role in shaping species composition in pelagic environments. In this review, we discuss and categorise strategies used by algicidal bacteria for the attack on microalgae. We highlight the complex regulation of algicidal activity and defence responses that govern alga–bacteria interactions. We also discuss how algicidal bacteria impact algal physiology and metabolism and survey the existing algicidal metabolites and enzymes. The review illustrates that the ecological role of algicidal bacteria is not yet fully understood and critically discusses the challenges in obtaining ecologically relevant data.

Keywords: plankton interactions; algicidal bacteria; lysis; algicides; food web

INTRODUCTION

The key players living in the Earths' oceans and lakes are photosynthetic unicellular microbes, and their associated bacteria, viruses and protist grazers. These organisms are found universally in freshwater and marine environments, from coastal zones to open water. Phytoplankton on average accounts for ~50% of global primary production by photosynthetic activity (Behrenfeld *et al.* 2006). It also acts as a sink of inorganic nutrients that are mobilised upon predation or cell death and concomitant lysis. Plankton species composition on both macro- and microscale is affected by biotic interactions as well as by temporal and spatial fluctuations of nutrients, resources and temperature (Dann *et al.* 2016). It is estimated that up to 90% of phytoplankton-derived organic matter is recycled by heterotrophic bacteria within the microbial loop (Azam *et al.* 1983). Such high turnover rates of phytoplankton biomass substantially impact the balance of biomass formation and respiration in aqueous systems (Bidle and Falkowski 2004). Perpetual changes in species abundance and community assemblages are shaping the plankton communities over time. These dynamic processes are often driven by intra- and interspecies interactions. Heterotrophic bacteria, for instance, can dwell on resources excreted by living phytoplankton cells or resources released after algal cell death and lysis (Bidle and Falkowski 2004). These heterotrophic bacteria can follow different trophic strategies as a response to resource availability resulting in chemical niche specialisation (Hunt *et al.* 2008; Hansell *et al.* 2009; Kujawinski 2011; Mayali *et al.* 2014). During a phytoplankton bloom (a massive algal proliferation event driven by e.g. light, temperature and nutrient availability), the algal-associated microbial community can shift from being dominated by oligotrophic Alphaproteobacteria to copiotrophic Flavobacteria that

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grow on senescent algae and to Gammaproteobacteria that profit from products released by the degradation of algal biomass (Teeling *et al.* 2012; Ruff *et al.* 2014). Nutrient exchange is frequently the driver of alga–bacteria interaction, irrespective of whether the relation is symbiotic or opportunistic. Field observations suggest that phylogenetic diversity and specificity of bacteria is correlated to phytoplankton groups (Jasti *et al.* 2005; Bunse *et al.* 2016) or even to phytoplankton species (Pinhassi *et al.* 2004; Amin *et al.* 2015). In an impressive, comprehensive study of reoccurring patterns in bacterioplankton dynamics, metagenome analyses revealed recurrent patterns at the functional level, in particular with respect to algal polysaccharide degradation genes. It was concluded that despite variability between spring phytoplankton blooms, the succession of bacterial clades is driven by deterministic principles such as substrate-induced forcing (Teeling *et al.* 2016).

Within this review, we specifically focus on the group of algicidal bacteria that inhibit microalgal growth or actively lyse unicellular algae. Other algicidal microorganisms that are not considered in this review have been the subject of intensive studies and of reviews, including work on viruses (Tomaru *et al.* 2008; Rohwer and Thurber 2009; Martiny *et al.* 2014) or fungi (Gerphagnon *et al.* 2015). The investigation of the strategies of algicidal bacteria is of substantial interest for scientists from diverse fields including biogeochemistry, algal physiology, ecology and environmental sciences, and aspects from all these disciplines will be covered here. In addition, several applications of algicidal bacteria in biotechnology and environmental engineering are currently under development. These are not the subject of this contribution but are reviewed elsewhere: current and potential applications of algicidal bacteria in biofuel production are reviewed in the study by Wang *et al.* (2016b). For such purposes bacteria might be used to stimulate high-value product formation, to support harvesting by promoting cell aggregation or to perform cell lysis thereby reducing energy-intensive processing. The specific use of algicidal microorganisms and algicides to induce microalgal cell disruption for biomass processing is specifically addressed in a review by Demuez, Gonzalez-Fernandez and Ballesteros (2015a). Natrah *et al.* (2014) summarised the role of alga–bacteria interactions in aquaculture. The potential to control harmful algal blooms using algicidal bacteria is discussed in several recent reviews (Gumbo, Ross and Cloete 2008; Kim *et al.* 2008; Jancula and Marsalek 2011; Seong and Jeong 2013; Shao *et al.* 2013). We also want to refer here to review articles on specific organismic groups or species that include aspects on the impact of algicidal bacteria. Reviews with a focus on cyanobacteria (Dahms, Ying and Pfeiffer 2006; Leflaive and Ten-Hage 2007; Van Wichelen *et al.* 2016), diatom–bacteria interactions (Amin, Parker and Armbrust 2012) or *Pseudoalteromonas* spp. (Holmstrom and Kjelleberg 1999) are noteworthy in this context. In this review, we exclude the numerous studies that claim the investigation of algicidal bacteria or algicides without any ecological rationale. Here, metabolites are introduced that either are not occurring in the environment in relevant concentrations or the interactions of species are investigated that would never encounter in nature. While these studies might be useful for biotechnological purposes, they do not contribute to the ecological and functional understanding of algicidal activity in the plankton, which is in the focus of this contribution.

A most influential review defining the field has been published in 2004 by Mayali and Azam; it summarises nicely the state of research at that time and systematically defines ways to consider ecological relevance in such plankton interactions (Mayali and Azam 2004). Examining the Mayali review, it becomes evident that substantial progress has been made, mainly driven by field and mesocosm experiments, genetic methods, elaborated bioassays and advances in chemical analytics. In this contribution, we focus on this progress with a special emphasis on emerging possibilities to address algicidal bacteria within their natural environment. We place special emphasis on algicidal metabolites, regulation of the interaction between algicidal bacteria and their target organisms and the ecological consequences of alga–bacteria interaction.

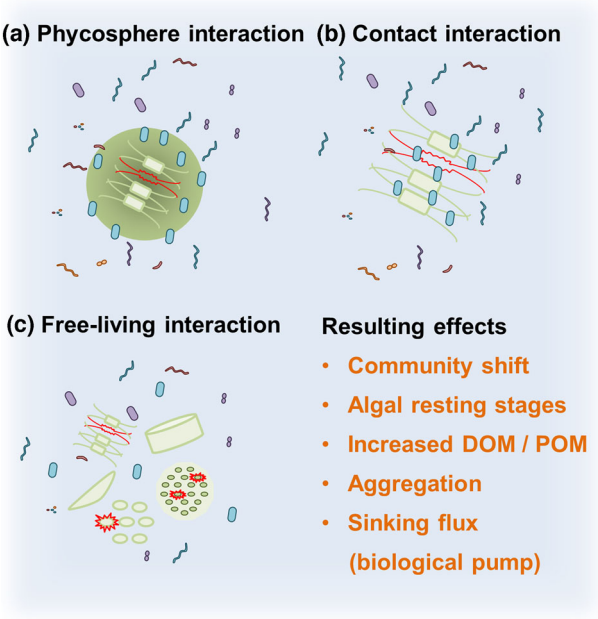

Figure 1. Types of association of algicidal bacteria with phytoplankton. (a) Algicidal bacteria (in blue) can operate in the immediate DOM-enriched vicinity of algal cells (phycosphere, in green). (b) Activity of algicidal bacteria can be observed upon direct cell-cell contact with the target organism. (c) Bacteria might also be active in populations where they are not associated with specific algae. Red cells indicate algal lysis by bacteria. The effect of algicidal bacteria within the photic zone and their influence on export processes are listed.

Scales of interactions

It is often suggested that algicidal bacteria have a massive impact on the productivity of aquatic systems by modulating entire communities even if, as outlined below, solid experimental prove for this hypothesis is difficult to obtain. Most yet described algicidal bacteria are lytic to phytoplankton and are frequently succeeding algal blooms of diatoms, coccolithophores, *Phaeocystis* spp. as well as often toxic species belonging to the groups of dinoflagellates and raphidoflagellates (Demuez, Gonzalez-Fernandez and Ballesteros 2015a). These bacteria can interact with freely floating unicellular or colonial algae, but considerations of concentrations in the open water make it likely that excretion of active algicidal metabolites would only be a feasible strategy during conditions with high cell densities (Fig. 1). It can be thus argued that interactions between freely floating organisms might not be very widely distributed.

Interactions in the phycosphere

The coupling between primary phytoplankton production and secondary production by heterotrophic bacteria creates a very heterogeneous environment (Azam and Malfatti 2007). Observed

spatial heterogeneity is often driven by the formation of microbial clusters around nutrient patches and gradients. Such three-dimensional and temporal niches can originate from the influx of nutrients from terrestrial environments, from exudates of larger organisms, cell lysis and many other events, thereby creating highly productive hotspots. Independent of the nature of alga–microbe interactions, the regions around algal cells that are termed 'phycosphere' have to be considered (Fig. 1) (Bell and Mitchell 1972). The phycosphere is mainly enriched with fixed carbon contributed by the algae but also signalling compounds and allelochemicals can accumulate within this zone. It creates a high-nutrient, semiprotected area in which mass transport is limited to diffusion and not influenced by turbulence. The underlying reasons for creating such specific nutrient-rich surroundings by phytoplankton are diverse but not fully understood. The exudates can function as a chemical defence (Dutz, Breteler and Kramer 2005) or provide allelochemical activity (Van Donk 2007), but excretion of organic matter has also been linked to photoprotection (Cherrier *et al.* 2015) and protection against heavy metal stress (Strmecki *et al.* 2010). Excreted dissolved organic carbon (DOC) might also mediate mutualistic interactions with non-algicidal bacteria (Aota and Nakajima 2001) and even symbiotic trophic interaction between bacteria and phytoplankton is regulated within the phycosphere (Wagner-Döbler and Biebl 2006; Armbrust 2009; Geng and Belas 2010; Amin, Parker and Armbrust 2012; Cooper and Smith 2015; Kouzuma and Watanabe 2015; Ramanan *et al.* 2016). The composition of algal exudates varies between phytoplankton species and even between growth phases of one species, thereby challenging the adaptive capabilities of bacteria (Barofsky, Vidoudez and Pohnert 2009; Weber *et al.* 2013). In accordance, growth efficiency and metabolic activity of heterotrophic bacteria can be dynamically influenced by such algal exudates (Azam and Malfatti 2007; Sapp *et al.* 2007; Natrah *et al.* 2014). On the other hand, it has also to be considered that algae generate a chemical 'fingerprint' that might guide motile bacteria towards nutrient hot spots. Since the use of carbon derived from phytoplankton differs among bacterioplankton, the specific excretions will directly influence bacterial community composition (Sarmento and Gasol 2012).

Due to methodological restrictions arising from the analysis of unicellular algae, the direct demonstration of chemical gradients within the phycosphere is difficult. The monitoring of this zone and studies how it shapes the associated microbiome has mainly been done with macroalgae and biofilms as study objects (Grosser *et al.* 2012; Saha *et al.* 2014). Recently, a very elegant study revealed spatiotemporal patterns of bacteria around individual *Chaetoceros affinis* diatoms that can be clearly explained with a response to a phycosphere (Smriga *et al.* 2016). By combining video microscopy and modelling, the role of bacterial chemotaxis in the resource exploitation around lysed algal cells could be explained. It can thus be regarded as established fact that secretions of unicellular algae provide noticeable amounts of dissolved organic matter (DOM) to the outside environment and these carbon hotspots are valuable resources for bacteria that would elsewhere have to deal with much more oligotrophic conditions (Amin, Parker and Armbrust 2012). To enter the phycosphere, bacteria are dependent on encounters. Encounter rates can be increased by directed motility (Barbara and Mitchell 2003; Xie *et al.* 2011), and the duration of an interaction can be increased by association with the phytoplankton cells by adhesion (Grossart *et al.* 2005; Slightom and Buchan 2009; Grossart 2010). Colonisation can lead to complex associations of both photoautotrophs and heterotrophs that are often surrounded by a joint polysaccharide dominated matrix (Fig. 1). Ultimately, the microbiome may be vertically transmitted to subsequent generations relieving the bacteria of the need of anew encounters. Bacterial successions within high-productive areas such as the phycosphere are thus generally governed by physiological and behavioural responses of the bacteria. Complex signalling chemistry involving specific chemoattractants or quorum sensing (QS) regulators can mediate these processes (Cooper and Smith 2015). Consequently, heterotrophic bacteria have to cope with diverse settings and have developed means to actively shape their environment. The diverse interaction situations in the plankton and the phycosphere have surely contributed to the evolution of a multitude of adapted algicidal strategies.

Algicidal bacteria and their lifestyle

Most known algicidal bacteria belong either to the phyla Bacteroidetes or Gammaproteobacteria (such as *Alteromonas*, *Pseudomonas* and *Pseudoaltermonas*) but algicidal Alphaproteobacteria are also reported (Kirchman 2002; Goecke *et al.* 2013). Only a minority are Gram positive such as members of the phylum Actinobacteria and the genus *Bacillus* (Firmicutes) (Mayali and Azam 2004; Zhou *et al.* 2015). Isolates of algicidal bacteria have been obtained from diverse regions of the oceans; in fact, surface waters (e.g. Jung *et al.* 2008), algal bloom samples (Park *et al.* 2010) and sediments (Lenneman, Wang and Barney 2014) are rich reservoirs. These bacteria have adapted their strategies to the diverse aqueous environments. Based on the available data, it is however hard to predict under which situations or in which environments the prevalence of algicidal bacteria is highest. DeLong, Franks and Alldredge (1993) observed that the bacteria in macroaggregates and marine snow are dominated by algicidal *Cytophaga* (Bacteroidetes) and Gammaproteobacteria. A systematic screening, however, is still lacking but first studies already point towards an increased hit rate in particle-associated compared to free-living bacteria and a generally low host specificity (Park *et al.* 2010). This is in agreement with the observation that nutrient shuttling between algae and bacteria is the basis for these microbial interactions. A high nutrient availability as it is found in the phycosphere is often a prerequisite for the production of algicides. Under laboratory conditions, algicides are often released under optimised culturing conditions at high cell densities (Mayali and Doucette 2002; Roth *et al.* 2008). This mirrors an environmental situation with increased algicide expression rates at later phytoplankton bloom phases or in nutrient hotspots. The observed preferred algicide production at high cell densities might be additionally explained with the involvement of bacterial QS mechanisms controlling algicide production in a density-dependent way (Williams *et al.* 2007). Interestingly, a change in lifestyle depending on the nutrient availability or cell density has been observed for bacteria that can switch from an algicidal to a symbiotic strategy (Amaro *et al.* 2005; see also section Regulation).

The variety of microbial strategies to take advantage of algal primary production is remarkable. Besides the use of algal exudates as a resource, microbes can also actively modulate algal activity and performance to increase their supply of nutrients. Two fundamentally different lines of attack have been identified. One is only effective in situations where direct contact or close proximity of the algicidal bacteria with the host organism is found (Fig. 1). The other relies on the indirect interaction via excreted diffusive algicides. The contact-based algicidal activity has been shown for numerous bacteria (see for example Wang *et al.* 2005; Roth *et al.* 2008), whereas examples for non-contact interactions are less frequently reported (Paul and

Pohnert 2011; Li, Geng and, Yang 2015). Even unusual modes of action have been observed; for example, a freshwater *Saprospira* sp. (Bacteroidetes) forms bundle-like structures that are suspected to be involved in catching cyanobacterial prey before lysis (Shi *et al*. 2006). The most drastic way how algicidal activity is manifested is clearly the lysis of algal cells. Other activities that are also summarised under the concept of algicidity include the induction of morphological changes, growth inhibition modulated by excreted factors or nutrient competition as well as the immobilisation of previously mobile algae (Wang *et al*. 2005; Mu *et al*. 2007; Bai *et al*. 2011; Lenneman, Wang and Barney 2014; Demuez *et al*. 2015b; Li *et al*. 2016).

Specificity of algicidal bacteria

The specificity of algicidal activity is a central topic if environmental engineering by the addition of bacteria is envisioned. Investigation of specificity also offers opportunities to understand the mode of action of algicides and their targets. As a consequence, many studies survey for algicidal activity using a broad selection of algal test organisms. Specificity is commonly characterised by toxic threshold concentrations but unfortunately, most of these experiments are not comparable since the species tested are arbitrarily selected and the assays are not standardised. Many algicidal bacteria show a broad host range and inhibit or lyse microalgae from different phyla (Skerratt *et al*. 2002; Roth *et al*. 2008; Park *et al*. 2010). Others are only active against specific groups or certain species. However, even within species selectivity was observed with an algicidal bacterium from the phylum Bacteroidetes. It was active against three *Karenia brevis* isolates while six other isolates of the same species were unaffected. The same bacterium was also active against two out of five *Alexandrium* isolates indicating a highly random, unexplained specificity (Roth *et al*. 2008). Park *et al*. (2010) surveyed patterns of algicidal specificity and observed that 231 of 487 particle-associated bacterial strains were algicidal while only 55 of 249 free-living bacterial isolates showed activity. Interestingly, 80% of particle-associated strains could kill multiple algal species, whereas 75% of the isolates of free-living bacteria killed only one of the six tested dinoflagellates and raphidophytes. If this pattern universally holds true, this finding might support strategies for the isolation of host-specific bacteria.

In the case of *Cytophaga* sp., results on algicidal specificity in lab experiments could indirectly be linked to field observations. The *Cytophaga* sp. was initially isolated during the bloom of the harmful red tide alga *Chattonella antiqua*. In laboratory co-incubation experiments, it was proven to be rather unspecific and lysed diatoms, dinoflagellates and raphidophytes (Imai, Ishida and Hata 1993). This lack of specificity was also reflected in the bacterial abundance during field surveys. *Cytophaga* concentrations reached highest values after the peak of *C. antiqua*. However, the abundance of this algicidal bacterium also followed the total amount of microalgal biomass even when *C. antiqua* was absent, indicating that in field situations, it can also profit from resources provided by a wider selection of algae (Imai *et al*. 2001). Several promising results have been obtained from studies on mixed species assemblies in micro- and mesocosms. An important set of experiments demonstrating nicely the effects on entire communities was performed with an algicidal bacterium *Shewanella* sp. (Gammaproteobacteria). Extracts of this bacterium are specifically algicidal against dinoflagellates, while a chlorophyte, a cryptophyte and a diatom tested were not affected (Pokrzywinski *et al*. 2012). The active extract exhibited photosystem II inhibition and induced loss of cell membrane integrity but no conclusive cellular targets could be identified (Tilney *et al*. 2014b). In mixed laboratory microcosms initiated from three natural dinoflagellate blooms, the *Shewanella* extract resulted in decreased effects in communities compared to unicellular cultures. The entire eukaryotic community composition was, however, shifted to increasing proportions of heterotrophic protists. Diatom abundance also increased at low algicide concentrations. In addition, ciliate abundance, as well as a bactivorous chrysophytes, increased (Tilney *et al*. 2014a). This shift toward communities dominated by heterotrophic and bacterivorous organisms is often observed in treatments using algicidal bacteria. Remarkably, in the study cited the effect was also observed in the absence of algicidal bacteria after treatment with the algicidal extract. This observation points towards a determining effect of the organic substances released upon cell lysis. Another example of the effect of specific algicides was reported by Jung *et al*. who identified a *Pseudomonas fluorescens* strain that was introduced as a candidate for the control of the freshwater diatom *Stephanodiscus hantzschii*. In indoor mesocosms with natural species assemblies collected during an *S. hatzschii* bloom, they confirmed the reduction of this alga by 88% while the amount of other phytoplankton remained unaffected (Jung *et al*. 2008). A remarkable specificity was also observed during microcosm incubations with a not further characterised algicide extracted from the actinobacterial *Streptomyces alboflavus* (Cai *et al*. 2016). This algicide is active against *Phaeocystis globosa* and could remove this species from microcosms without affecting others. Exposure to the algicide led to the instant increase of the plasma membrane permeability and disruption of the photosynthetic system, but these activities could not explain the underlying mode of specificity.

Regulation of algicidal interactions

It can be hypothesised that pronounced regulation of activity will be required for bacteria to maintain efficient algicidal strategies in an environment with spatial and temporal heterogeneity. On the other hand, algae might respond with induced resistance or even defence mechanisms against the attacker in situations with fluctuating pathogen pressure. Only a few pioneering studies have reported on ecologically relevant regulated interactions between algicidal bacteria and host algae. Besides dilution effects, a complicating factor in environmentally realistic studies is the complexity of consortia with multiple species that might interact in a complex network. In the following, concepts and, if available, first examples of regulation during interactions will be introduced.

Chemotaxis

Finding of prey species might be supported by the chemotactic behaviour of some bacteria, directing them along chemical gradients towards microalgae (Fig. 2a). In most reported cases, a positive chemotaxis could be observed, leading the organism to higher concentrations of the signal (Sonnenschein *et al*. 2012; Smriga *et al*. 2016). Thus, for example, Li *et al*. (2016) could demonstrate in a comprehensive study that *Chitinimonas prasina* (Betaproteobacteria) behaves chemotactically towards the diatom *Thalassiosira pseudonana*. Chemotaxis of the flagellated cells is directed towards the algae via a yet unknown cue and upon encounters the cells adhere on the algae with their flagella. The bacterium uses chitinases to metabolise chitin from the cell walls of diatoms. Chitin digestion leads to loss of cell integrity in the diatoms and supplies the bacteria with nutrients and

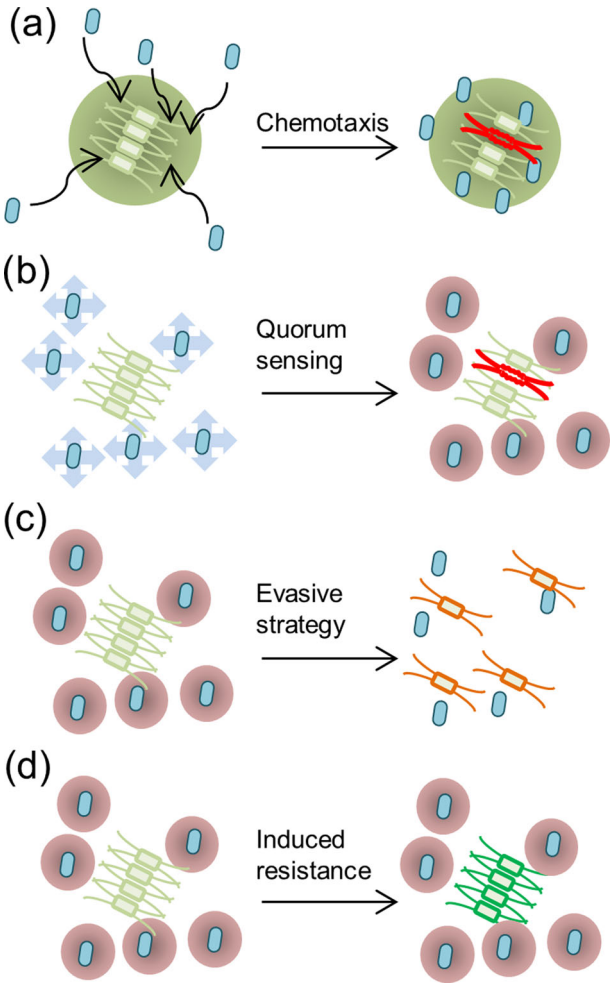

Figure 2. Modes of interactions between algicidal bacteria and their host. (**a**) Chemotaxis-mediated finding behaviour might guide algicidal bacteria to the host cells. The red cells indicate algae affected by algicidal bacteria. (**b**) QS chemicals (blue arrows) might trigger algicide formation (red circles) and as a consequence cell lysis. (**c**) Algae might form resting stages (orange cells) that are not targets of algicidal bacteria. (**d**) Upon perception of algicides or other signals from bacteria (red circles) resistance is induced in algae that subsequently survive even in the presence of algicides (this physiological or metabolic change is indicated by the darker colour of the cells).

energy. Contact between bacteria and the algae is a prerequisite for algicidal activity. Interestingly, all tested diatoms besides *Phaeodactylum tricornutum* were lysed, which is in accordance with the observation that this is also the only diatom that lacks chitin in its cell walls.

Nutrient cues

Nutrient availability could also be a possible cue to trigger algicide production in bacteria. However, evidence for such mechanisms is very limited and rather indirect. This lack of knowledge might be attributed to the difficulty to keep bacteria under fully nutrient-deprived conditions, which would be a pre-requisite for further experiments on the topic. This experimental limitation might explain that such mechanisms have only been reported for the cyanobacterium *Oscillatoria laetevirens*, where algicide production is regulated by nutrient availability (Ray and Bagchi 2001). Under conditions that limit growth (e.g. ammonia as N-source or phosphate limitation), stimulated algicide production was observed while in optimum growth conditions (e.g. organic N-source) the algicide production was abolished.

Quorum sensing

The cell-to-cell communication at both intra- and interspecies level is another factor to be considered if the dynamics of algicide production is concerned. The mechanism of concentration-dependent cell-to-cell-communication called QS was first studied with the marine Gammaproteobacterium *Vibrio fischeri* (*Aliivibrio fischeri*) nearly 40 years ago by Nealson and Hastings (1979). They showed that the bacterial enzyme luciferase responsible for bioluminescence occurred only at high cell densities and is under the control of secreted autoinducer signalling molecules. Bacterial behaviour regulation under the concentration-dependent regulation by autoinducers was in detail described in reviews by Bassler (Bassler 1999; Waters and Bassler 2005). QS is used by bacteria to initiate processes with high energy or resource costs only when they are beneficial to the population (Keller and Surette 2006). Gram-negative bacteria use not only acylated homoserine lactones (AHLs) as autoinducers (Fuqua and Greenberg 2002) but also 4-quinolon amide (Pesci *et al.* 1999; Mashburn-Warren *et al.* 2008), fatty acids and fatty acid methyl ester with similar function were reported (Deng *et al.* 2010). In planktonic Gram-negative and Gram-positive bacteria, furanone complexes (AI-2) also induce genetic expression (Skerratt *et al.* 2002; Williams *et al.* 2007). Due to their lifestyle in a highly diluted changing environment, it has early been postulated that algicidal bacteria regulate their activity by means of QS. However, until now, only a few studies were able to unambiguously prove the connection of the two processes (Fig. 2b). An indirect evidence for QS-type regulation of algicidal activity was provided by Nakashima *et al.* (2006b). They show that a prodigiosin-type pigment PG-L-1 (see section Alkaloids), isolated from a Gammaproteobacterium, has algicidal activity against various red tide phytoplankton species. The production of the pigment PG-L-1 is completely inhibited in the presence of erythromycin or chloramphenicol but can be recovered by the addition of AHLs. This induced production and the fact that the pigment production was inhibited by beta-cyclodextrin, an inhibitor of QS activities, are in fact pointing towards a control of prodigiosin production by QS. Other marine Gammaproteobacteria such as *Serratia* sp., *Pseudoalteromonas bacteriolytica* and *V. ruber* also produce prodigiosin-like pigments (Lewis and Corpe 1964; Sawabe *et al.* 1998; Shieh *et al.* 2003). For *Serratia* sp., production is also controlled by AHLs (Thomson *et al.* 2000). The investigation of the exometabolome of the marine *P. piscicida* revealed the bacterial signalling molecule to be 2-heptyl-4-quinolone (see section Alkaloids). This metabolite is not only a QS mediator, but also induces slow lysis in three strains of *Emiliania huxleyi* at biologically relevant nanomolar concentrations (Harvey *et al.* 2016). The quinolone thus mediates cross-kingdom interactions that can shift the phytoplankton population dynamics and trigger the intraspecies cell-to-cell communication (Diggle *et al.* 2007; Dubern and Diggle 2008). Paul and Pohnert (2011) studied the lytic activity of *Kordia algicida* (Bacteroidetes) on the diatom *Skeletonema costatum* and found that a concentration-dependent growth-inhibiting or lytic effect of the bacteria was caused by diffusible substances. Further tests showed that the algicidal agent is a protease (see section Enzymes) released by the bacteria. Induction with the spent medium of dense *K. algicida* cultures led to an increased protease release, which is a first evidence for a QS-regulated process. Further studies are however necessary to identify the mode of regulation in this system.

Quorum quenching

In general, the use of signal molecules for the control of vital functions makes the producer susceptible to development of resistance or to interference strategies targeting the signal molecules (reviewed in Grandclement *et al.* 2016). There is much evidence from marine bacteria that they employ so-called quorum quenching (QQ) strategies in which QS signalling is suppressed. Identified mechanisms include the inactivation of *N*-acyl homoserine lactones by lactonases or by cleavage of the amide bond through the action of acylases (Yates *et al.* 2002; Romero *et al.* 2008; Safari *et al.* 2014). Some bacteria and microalgae are also able to locally raise the pH which can affect the stability of QS molecules in their surroundings (Yates *et al.* 2002). There are several examples for QQ in the marine environment (Romero, Martin-Cuadrado and Otero 2012). Especially in dense marine microbial communities, such as sediments, biofilms and on surfaces of algae, a large number of marine bacteria interfering with AHL signalling could be found (Romero *et al.* 2011). A broader survey revealed that 84 isolates out of 464 from estuarine and oceanic water (0 and 10 m depths) are able to interfere with C6- and C10-AHL signalling. Prevalence of QQ mechanisms is lower in estuarine isolates (2% of the investigated samples) than in oceanic samples (28%) (Romero, Martin-Cuadrado and Otero 2012). Given this wide distribution, it will be of interest to specifically address the effect of QQ on algicidal mechanisms. Especially in the close contact situations within the phycosphere, biofilms or marine snow such mechanisms might become relevant. Several microalgae have also developed strategies for QQ or QS inhibition, but up to now no direct link to interference mechanisms with algicidal activity is reported. The diatom *Nitzschia cf. pellucida*, for example, produces a haloperoxidase which deactivates bacterial β-keto-AHL QS molecules. The disruption of these signal molecules is H_2O_2 dependent (Syrpas *et al.* 2014). The alga also produces the secondary metabolite cyanogen bromide that is catalysing the cleavage of peptide bonds as they occur in AHLs (Vanelslander *et al.* 2012). The unicellular green alga *Chlamydomonas reinhardtii* can secrete lumichrome that mimics AHLs from associated bacteria (Teplitski *et al.* 2004; Rajamani *et al.* 2008, 2011). The effects of 19 microalgal strains commonly used in aquaculture on QS-regulated gene expression of three reporter strains were studied. Two out of 19 tested algae inhibited the AHL-dependent pigment production in *Chromobacterium violaceum* (Betaproteobacteria). Reduced green fluorescent protein production in a QS-controlled reporter strain *Escherichia coli* was observed with six algae (Natrah *et al.* 2011). Again, this broad distribution of complex signalling event prompts further investigation in the field of algicidal bacteria.

Evasive strategies

Evasive strategies are another possible form of resistance against algicidal activity. Algae have means to form morphologically distinct resting stages as a survival strategy that could potentially be employed to avoid contact with algicidal bacteria (Fig. 2c) (Anderson and Rengefors 2006; Mertens *et al.* 2012). Once the conditions ameliorate, these resting stages can fuel a novel generation of proliferating algae. However, this interaction mechanism is purely theoretical since to our knowledge, no experimental evidence for the mechanism has been provided till to date. In general, marine bacteria can however induce such resting stages. *Roseobacter* sp. (Alphaproteobacteria), for example, induces cyst formation in the dinoflagellate *Alexandrium tamarense* that is suspected to play an important role in bloom dynamics (Adachi *et al.* 1999). Whether this *Roseobacter* sp. exhibits algicidal activity is however not proven.

Induced resistance

A first example for an induced resistance against algicidal bacteria has been found in the diatom *Chaetocerous didymus*. This alga was the only resistant diatom in a screening performed with the algicidal bacterium *K. algicida* (Fig. 2d) (Paul and Pohnert 2011). Interestingly, the resistance of the algae goes ahead with an induced production of own proteases that are suspected to counteract the lytic enzymes of the bacteria (Paul and Pohnert 2013). These proteases are substantially more effective compared to the bacterial counterparts and can not only be triggered by the bacteria but also by signals contained in the >30 kDa fraction of a bacterial culture filtrate.

Complex interactions

A more complex interaction, potentially involving multiple regulators, has been identified in the Alphaproteobacterium *Phaeobacter gallaeciensis* (Seyedsayamdost *et al.* 2011b). The 'Jekyll-and-Hyde' chemistry of this bacterium illustrates impressively that assigned functions of key organisms might change dramatically in a context-dependent way. *P. gallaeciensis* is a bacterium that interacts with the bloom-forming coccolithophore *E. huxleyi*. In situations where the *E. huxleyi* bloom is growing, *P. gallaeciensis* produces the auxin phenylacetic acid and the broad-spectrum antibiotic tropodithietic acid that support the development of the alga. However, once the algal bloom decays, the bacterium switches its lifestyle to an algicidal type. It releases the potent and selective roseobacticides that lyse the aging algae. The master switch triggering this dramatic change is *p*-coumaric acid, a lignin degradation product released by aging algae (Seyedsayamdost *et al.* 2011b). *p*-Coumaric acid also triggers the production of a putative 226 g mol^{-1} roseobacticide that causes loss of motility and cell enlargement in phytoplankton (Sule and Belas 2013). Other highly complex interactions take place in the phycosphere of the dinoflagellate *A. tamarense*. In the presence of associated Alpha-, Beta- and Gammaproteobacteria, the growth of the alga is suppressed. The dinoflagellate, however, associates closely with the small flagellate alga *Ochromonas* sp. that ingests bacteria. This interaction, entirely taking place in the phycosphere, relieves bacterial pressure from the dinoflagellate and restores growth (Hu *et al.* 2015). Cascading effects are also to be considered since alga-associated microbial communities might modulate the potency of algicides (Mayali and Doucette 2002; Roth *et al.* 2008).

Algae are also supposed to be able to fend off algicidal bacteria by means of antibiotics. Most antibacterial metabolites were, however, found from marine microalgae by using cell lysates or extracts (Desbois, Mearns-Spragg and Smith 2009; Michalak and Chojnacka 2015) and thus the evaluation of their true ecological function is difficult. A compound class that has been highly investigated in this context is the oxylipin family from diatoms that are predominantly released upon cellular disruption but also within defined events during regular growth in cultures and the field (Vidoudez and Pohnert 2008; Vidoudez *et al.* 2011a, b). Especially the polyunsaturated aldehydes produced by many diatoms have antibacterial activity (Adolph *et al.* 2004; Ribalet *et al.* 2008; Balestra *et al.* 2011), comparable to similar metabolites found in higher plants (Blée 2002). These data suggest a possible defence mechanism of diatoms against microorganism including algicidal bacteria but the connection has not been shown in field studies till to date.

Bacteria–bacteria interactions are widely studied for members of the Roseobacter clade, which produce antibacterial substances potentially providing a competitive advantage e.g. during surface colonisation of macroalgae (Manefield *et al.* 2002; Rao, Webb and Kjelleberg 2006; Nissimov, Rosenberg and Munn 2009; Goecke *et al.* 2010; Berger *et al.* 2011; Cude *et al.* 2012; Cude and Buchan 2013; Dang and Lovell 2016). Principles within bacterial competition are reviewed by Hibbing *et al.* (2010). Long *et al.* (2003) linked production of antibiotic compounds by a particle-associated *Alteromonas* sp. to a multitude of functions as the metabolites shape not only the species composition of the bacterial community in a model particle system but they also inhibit growth of one cyanobacterium and three diatoms.

The complexity of the observed interactions and the close association of the involved organisms suggest that some algicides, especially those with known antibiotic activity, might also affect the microbial community and consequently also algal symbionts, resulting in the amplification of algicidal effects. On the other hand, alga-associated bacteria might also provide protection from algicidal bacteria either by the production of antibiotics or by metabolization of algicides. Since marine microbial communities are part of tightly connected networks, common investigations of bilateral interactions are most likely only scratching the surface of the hidden regulation of network dynamics (see also Amin *et al.* 2015).

Methods for the investigation of algicidal activity

The sections above make it clear that a truly ecologically relevant investigation of algicidal principles is highly challenging. In order to distinguish between algicidal activity mediated by contact interactions and by diffusible metabolites, bioassays can be performed by either infecting algae directly with bacteria or by treating them with bacterial exudates in cell-free spent medium (Fig. 3a and b). In order to circumvent overlaying effects of remaining medium, bacteria can be grown on agar plates and resuspended. However, care has to be taken since algicidal activity is often overlooked if it is under the control of signalling chemicals. In these cases, induction of the production of algicidal metabolites or QS-based upregulation of algicidal activity has to be performed before the generation of extract or cultures for bioassays (Fig. 3d and e). Non-contact co-culturing is an approach that covers both the above-mentioned mechanisms of regulation (Fig. 3c). It is also a reliable method to determine if an observed activity is dependent on cell–cell contact (Kim *et al.* 2009b; Paul, Mausz and Pohnert 2013). If algicidal activity in more complex communities is investigated, a potential additional overlaying effect of algal metabolites has to be considered. Conspecifics or other species in the experiment might be affected by allelochemicals released during bacteria-induced lysis. Furthermore, the concept of strictly separating direct and indirect modes of action is challenged by the existence of a mixed mode mechanism that includes both the requirement for direct contact and the excretion of a chitinase (Li *et al.* 2016).

Quantitative aspects

The above-mentioned methods are suitable for the identification of compounds with algicidal activity, and many studies are limited to this aspect. If the compounds, however, have a true ecological function can only be judged after their quantification in nature or in laboratory settings that provide close to natural conditions. Only if the active concentrations of isolated algicides fall in the range of the concentrations determined analytically, a true ecological function can be postulated. However, many of the below-mentioned metabolites are active in the micromolar range, thus in concentrations that rarely occur in nature, or, as it might be argued based on hydrodynamic considerations, that can only be reached in close contact situations where metabolites accumulate in the diffusion limited zone (the phycosphere) around cells of the algae (Breckels *et al.* 2011). Especially this phycosphere concept has attracted much attention since in fact most interactions of algae and their associated microbial consortia are occurring in direct proximity to the algal cells (Rolland *et al.* 2016). Lysis of *Alexandrium* sp., for example, is caused by bacteria from its phycosphere that is highly diverse in natural communities (Hasegawa *et al.* 2007; Wang *et al.* 2010). It is however extremely difficult to determine the actual concentrations of metabolites in the immediate vicinity of algal cells and mostly modelling approaches allow their estimation (Breckels *et al.* 2010). A first direct monitoring of the pigment fucoxanthin in the vicinity of macroalgal cells using Raman microscopy revealed that bacteria in the immediate vicinity of the algae will be exposed to millimolar concentrations of active metabolites, even if concentrations of the compound in the water are close to the detection limit (Grosser *et al.* 2012). Truly ecologically relevant investigations would thus have to consider not only bulk concentrations, but also the influence of gradients and the dimensions of the receiving organisms. Given the high concentrations that might accumulate within the phycosphere, some metabolites with moderate activity might play an important role locally. In addition, complexity is even increased since metabolites might change their function in a concentration-dependent manner, as it has been shown for indole-3-acetic acid. The bacterially produced phytohormone can promote both algal growth and algal death in a concentration-dependent manner thereby dynamically influencing performance of the microalga *E. huxleyi* (Segev *et al.* 2016).

Linking lab and field data

In the first view, the setup of most lab experiments with dense cultures contradicts the average situation in the plankton, where the typical abundance of the entire microbiome is comparably low (roughly 10^5–10^6 cells/mL and up to 10^7 cells/mL during a bloom). However, such cell densities are only average values and since microscale patches with locally increased biomass play an important role in plankton ecology, such hotspots might boost bacterial abundance even in the natural environment (Doubell, Prairie and Yamazaki 2014). A hitherto poorly addressed problem in the connection of field and laboratory work lies in the often purely correlative interpretation. Prevalence of algicidal bacteria is often high during a declining phytoplankton bloom phase but it is not clear if this is indeed linked to the lytic activity of bacteria (Skerratt *et al.* 2002). During declining blooms, the predisposition of algicidal bacteria for the efficient use of released nutrients resulting from cell lysis might already cause sufficient advantage leading to their dominance (Biddanda and Benner 1997; Azam and Malfatti 2007). Lab experiments often lead to the claim that algicidal bacteria can control phytoplankton blooms; however, this assumption is till to date not fully supported by field data. Chemical analysis of algicides in the field or transcriptomic monitoring of genes relevant for algicide production might help in the future to solve this issue.

Another still unresolved problem is the role of how to evaluate the influence of signalling chemistry in naturally occurring plankton communities. Such specific interactions often have been observed for mutualistic interactions, but even if there is evidence from lab data that algicidal bacteria use (secondary)

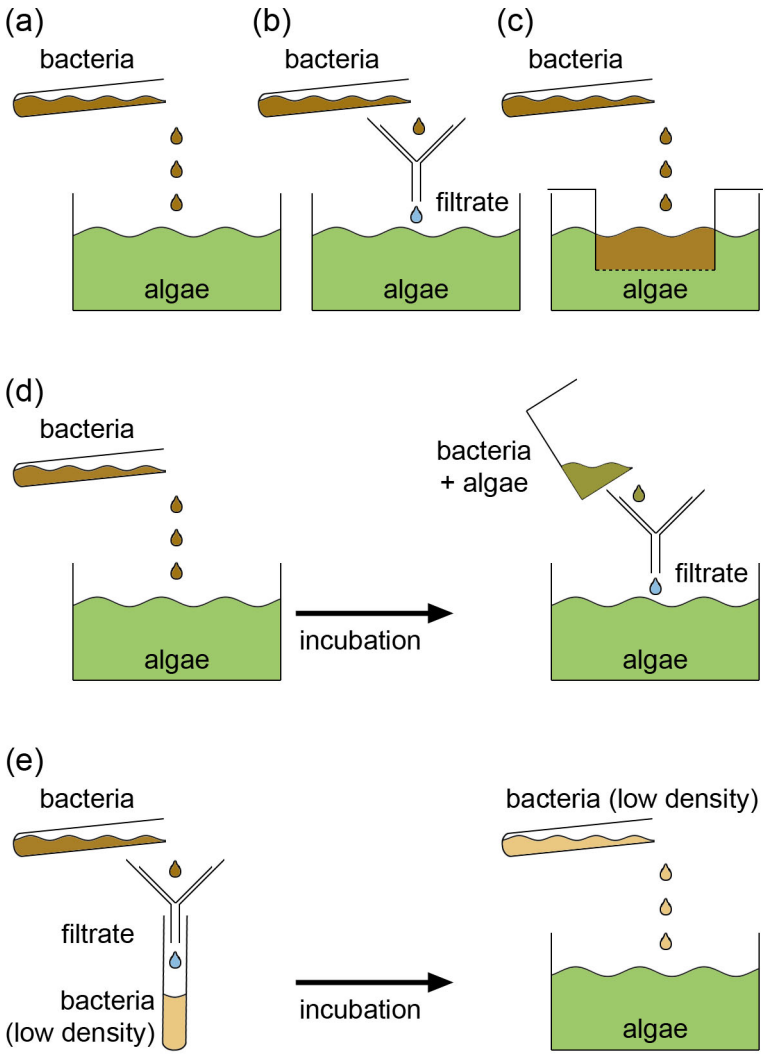

Figure 3. Methods for the elucidation of algicidal mechanisms and their regulation. (**a**) Cultivation with direct contact allows identification of algicidal bacteria independent of their mechanism of activity. (**b**) If cell-free spent medium (i.e. filtrate) is active, the mechanism involves excreted algicides. (**c**) To test whether cross-kingdom signalling is necessary for algicide production, non-contact co-culturing with semipermeable membranes facilitating passage of algicide but not of cells can be used. (**d**) Cross-kingdom signalling can be monitored after a period of cultivation with direct contact followed by testing the spent medium (i.e. filtrate) of bacteria-killed algae for algicidal activity. The latter approach has the disadvantage not to distinguish between bacterial algicides and toxic algal waste products. (**e**) To provide initial evidence for a QS-type mechanism algicide, production is stimulated in below quorum density cultures by addition of filtrate from a high-density culture. Algicidal activity of the low-density culture can be tested afterwards with one of the methods described (**a-d**). Care has to be taken regarding the material of filters (**b, d, e**) and membranes (**c**) in order to minimise loss of algicide by adhesion or inhibition of algicide passage through the membranes.

metabolites from their prey as cues field data are still not available (Seymour, Ahmed and Stocker 2009; Seyedsayamdost *et al.* 2011b; Li *et al.* 2016) (see section Regulation).

In field studies, it also remains difficult to distinguish if the dominance of an algicidal bacterium is truly due to its algicidal activity or rather due to its successful competition for nutrients or simple opportunistic effects. Often it remains unsolved if the occurrence of an algicidal bacterium is not rather coinciding with the decline of a bloom. The assignment of the emitter and target organism of a natural product in the field is as well very difficult. In fact, even the presence of algicidal compounds in the field has to our knowledge not consistently been demonstrated. A possible way to solve this lack of knowledge could involve transcriptomics data that record the upregulation of genes required for algicide production or a chemical analysis of the respective metabolites in the field. If the molecular targets of the algicides are known, transcriptomics or proteomics of the target algae could also indicate its effectiveness during the interaction. Such protocols are however still not routinely available for field samples even if progress in method development has been made (McCarren *et al.* 2010; Moustafa *et al.* 2010; Keeling *et al.* 2014; Wang *et al.* 2014, 2015; Amin *et al.* 2015; Balzano *et al.* 2015; Cooper and Smith 2015; Guo *et al.* 2016a).

Active components

The algicides produced by bacteria are very diverse in structure and mode of action. The metabolites span a wide range of polarity from polar amino acid derivatives to less polar fatty acids and their size spans several orders of magnitude. Algicides comprise small metabolites with molecular weights below 500 g mol^{-1}, intermediate molecular weight compounds like

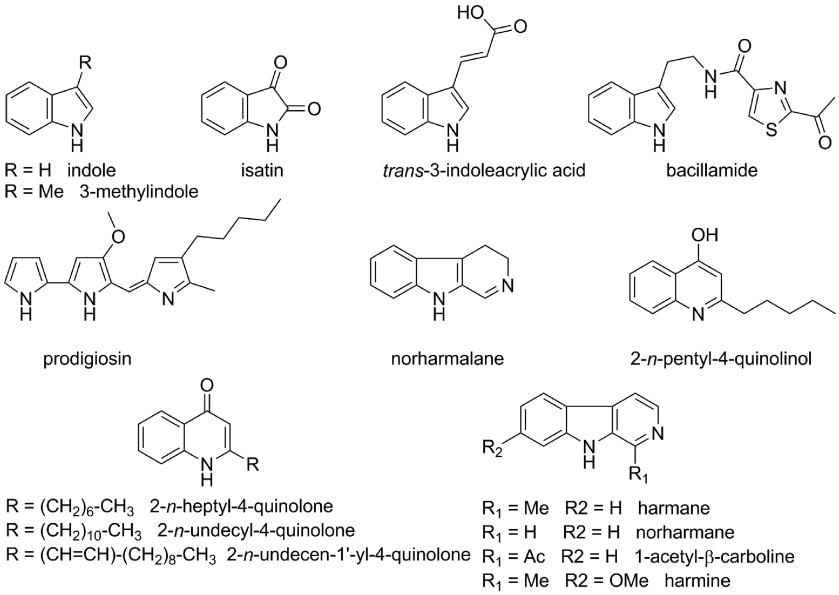

Figure 4. Structures of algicidal alkaloids.

peptides and even functional enzymes several kDa in size. This diversity is a major challenge for the structure elucidation of algicides. There are no universal extraction or separation methods that can be recommended. Algicide purification and structure elucidation has rather to start with optimised extraction procedures for the respective compound classes. In many cases, preliminary experiments that characterise the compound class of interest are required before extraction and purification are pursued. These can include heat or pH stress that denatures enzymes. Also, different extractions, e.g. liquid/liquid or solid-phase extraction can be undertaken to enrich algicides from the medium. Bioassay-guided fractionations with separation techniques that are optimised for the algicide classes are often the basis for the full characterisation (Prince and Pohnert 2010).

The structural diversity is also reflected in the multifaceted mode of action of algicides. Small metabolites generally have a defined target, e.g. the inhibition of an enzyme or the interaction with membranes, and therefore inactivate or disturb vital cellular functions of the host leading to cell death. On the other hand, enzymes catalyse biochemical transformations that lead to the degradation of the target organism. Mixed modes of action are also observed. The following sections will give an overview of the variety of algicidal metabolites and enzymes. We classified the active principles according to their biosynthetic origin or, when biosynthetic evidence is not obvious, based on common structural features. We exclude the numerous studies where claims of algicidal metabolites were made without any ecological rationale. Especially in the field of aquaculture and industrial applications, several structures from bacteria that do not occur in the plankton were brought forward that might act against microalgae. These metabolites can represent useful tools for biomass processing but are not ecologically relevant. We also do not list activities assigned to not fully characterised fractions or to primary metabolites administered in unrealistically high concentrations. However, as outlined above, the ecologically relevant concentrations are often not available for interacting plankton species and we thus can often not judge if algicidal metabolites are truly ecologically relevant. Algicides exclusively produced by cyanobacteria are excluded since they can rather be categorised as allelopathic. However, interesting parallels between bacterial and cyanobacterial algicides are highlighted. The following sections list identified principles but we do not validate the potential ecological role of the identified compounds.

Alkaloids

Alkaloids comprise a very diverse class of algicidal compounds (Fig. 4). The scaffolds include indoles, quinolones and others. The mechanism of algicidal activity of these nitrogen-containing metabolites with different biosynthetic origin is equally diverse.

Many algicides are derived from tryptophan and therefore belong to the class of indole alkaloids. Indole itself, isolated from a periphyton biofilm, inhibits the growth of cyanobacteria. This inhibition seems to be caused by impaired thylakoid membrane integrity, interrupted electron transport in photosystem II and reduction of the effective quantum yield (Wu *et al.* 2011). Another representative of the indole alkaloids is isatin, which was isolated from a marine *Pseudomonas* sp. as well as from a freshwater *Shewanella* sp. (Gammaproteobacteria) (Sakata, Yoshikawa and Nishitarumizu 2011; Li *et al.* 2014b). The growth of the diatom *Chaetoceros ceratosporum* is inhibited by isatin but not by indole (Sakata, Yoshikawa and Nishitarumizu 2011). Furthermore, isatin inhibits cyanobacterial growth (Li *et al.* 2014b). Cyanobacteria are also negatively affected by 3-methylindole produced by a freshwater *Aeromonas* species (Guo *et al.* 2016b). Production of 3-methylindole is regulated by QS (see section quorum sensing). Another anti-cyanobacterial indole derivative is trans-3-indoleacrylic acid produced by a *Rhodococcus* species (Actinobacteria) isolated from soil. Interestingly, a synergistic effect of trans-3-indoleacrylic acid and the co-isolated algicide L-pyroglutamic acid was observed (Wang *et al.* 2013). The indole moiety is also a structural element of other, more complex algicides like the indole-thiazole bacillamide. Bacillamide was isolated from a marine *Bacillus* species and is toxic against dinoflagellates and raphidophytes without affecting the tested diatoms, green algae or cyanobacteria (Jeong *et al.* 2003).

An important group of algicidal indole alkaloids are the tricyclic β-carbolines. Kodani and co-workers isolated harmane from an algicidal freshwater *Pseudomonas* species. Harmane as

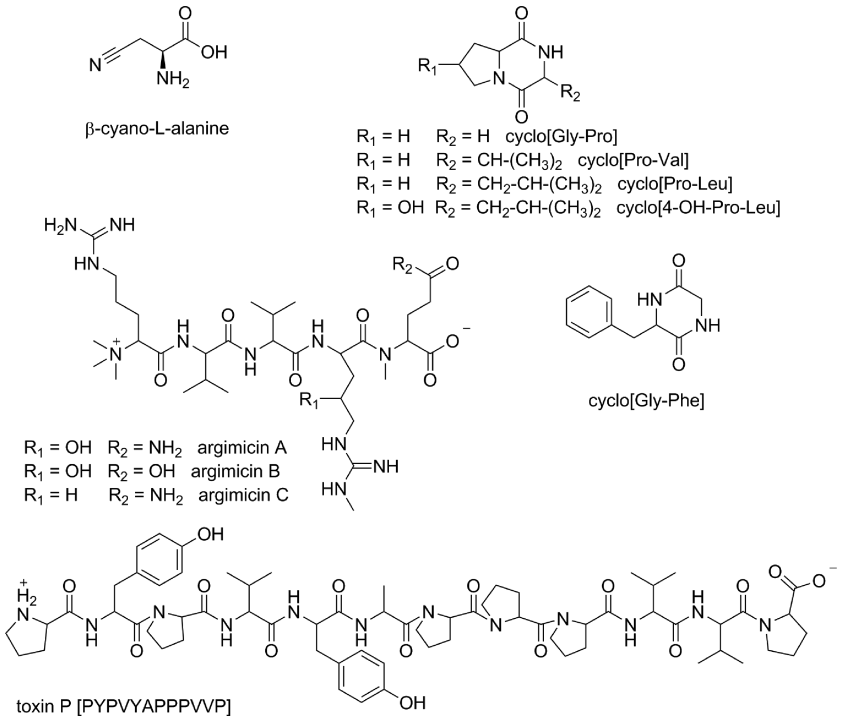

Figure 5. Algicidal amino acid-derived metabolites.

well as the structurally related norharmane inhibited the growth of various cyanobacteria, but not of two green algae species tested (Kodani *et al.* 2002). This specificity makes them potential control agents for harmful algal blooms. Harmine and norharmane, isolated from the freshwater *Bacillus flexus*, showed algicidal activity against cyanobacteria but not against green algae (Alamri and Mohamed 2013). A marine *Brachybacterium* species (Actinobacteria) is the source of 1-acetyl-β-carboline that inhibited growth of naked dinoflagellates and raphidophytes as well as of thecate dinoflagellates (Kim, Son and Jeong 2015). It is noteworthy that β-carbolines are also allelopathic toxins since they can be produced by cyanobacteria as well. The cyanobacterium *Nodularia harveyana* from brackish water produces norharmane and norharmalane with toxicity against several other cyanobacteria (Volk 2005, 2006). Comparing threshold activities of norharmane and norharmalane revealed that saturation of the double bond at position 3–4 leads to a decrease of cytotoxicity. Furthermore, comparison of these β-carbolines with harmane revealed lower minimal toxic quantities against some of the species tested due to the additional methyl group. The hypothesis that increased hydrophobicity might facilitate penetration through the plasma membrane is strengthened by the fact that in many cases the hydrophobic alkaloid base shows higher toxicity than the more hydrophilic hydrochloride (Volk 2006).

An example for a quinoline alkaloid algicide is 2-*n*-pentyl-4-quinolinol, which is produced by a marine *Pseudoalteromonas* species and a marine *Alteromonas* species. The antimicrobial activity of this compound also spans diatoms and cyanobacteria affecting not only growth, but also mobility and adhesive properties (Long *et al.* 2003; Wigglesworlth-Cooksey, Cooksey and Long 2007; Sakata *et al.* 2008). The structurally related compound 2-heptyl-4-quinolone was isolated from the marine *P. piscicida* and negatively affected growth rates of a coccolithophore, but not of a chlorophyte or diatom (Harvey *et al.* 2016). Another marine bacterium from the genus *Alteromonas* produces two algicidal pyrones (see section Others) as well as the quinolone alkaloids 2-undecen-1′-yl-4-quinolone and 2-undecyl-4-quinolone. Both compounds were more toxic to dinoflagellates and raphidophytes than to the green algae or haptophytes tested (Cho 2012). Compared to 2-undecyl-4-quinolone, the unsaturated double bond in 2-undecen-1′-yl-4-quinolone leads to an increased toxicity and the authors suggest more toxic oxidised hydroxyl compounds as a reason.

An example for an alkaloid algicide based on peptide precursors is the tripyrrole prodigiosin that has been detected in the marine Gammaproteobacterium *Hahella chejuensis* (Jeong *et al.* 2005; Kim *et al.* 2006; Zhang *et al.* 2016). Prodigiosin inhibits the growth of some dinoflagellates, a raphidophyte and a haptophyte. Another red pigment that was assigned to the prodigiosin family is produced by a marine Gammaproteobacterium. In contrast to many other algicides, this pigment reduces production of reactive oxygen species with a negative effect to the raphidophyte *Chattonella marina*, for which ROS production is essential (Nakashima *et al.* 2006a).

Amino acid derivatives, peptides and proteins

Numerous algicidal metabolites are structurally related to amino acids, although biosynthetic origin has not been studied in most cases (Fig. 5). A marine *Vibrio* sp. produces β-cyano-L-alanine inhibiting growth of several cyanobacteria, but not of green algae, diatoms or a dinoflagellate tested (Yoshikawa *et al.* 2000). A different mode of action has been observed in the freshwater *Stenotrophomonas maltophilia* (Gammaproteobacteria) that actively reduces the availability of nutrients that are essential for the target algae. The bacterium produces a hydroxamate-type siderophore that negatively affects cyanobacterial growth by limiting iron availability (Liu *et al.* 2014). It turns out that interactions via siderophore production and the accompanied

carbon-for-iron exchange are a common type of algal–bacterial interactions (Kurth *et al.* 2016).

Peptides and proteins can also have algicidal activity. A marine *Vibrio shiloi* strain, for example, produces a linear proline-rich dodecapeptide termed toxin P that inhibits photosynthesis in zooxanthellae isolated from corals only in the presence of ammonium ions (Banin *et al.* 2001). The authors conclude that the peptide might facilitate uptake of ammonia, which in turn uncouples photosynthesis. Photosynthesis also seems to be the target of argimicin A, a pentapeptide isolated from a freshwater *Sphingomonas* sp. (Alphaproteobacteria) (Imamura *et al.* 2000; Hibayashi and Imamura 2003). Argimicin A and the structurally related argimicins B and C inhibit growth of cyanobacteria without affecting green algae (Hibayashi and Imamura 2003; Yamaguchi *et al.* 2003). This is in accordance with the hypothesis that argimicin A inhibits photo energy transfer from phycobilisome, an accessory pigment complex of photosystem II in cyanobacteria (Hibayashi and Imamura 2003). So far uncharacterised is a potentially cyclic algicidal peptide produced by an *Alteromonas* sp. with diatom-lytic activity (Wang *et al.* 2016a).

Diketopiperazines are also a major class of bactericidal compounds. Apart from the indole alkaloid isatin (see section Alkaloids), the freshwater *Shewanella* sp. isolated by Li *et al.* (2014b) is also a source for hexahydropyrrolo[1,2-a]pyrazine-1,4-dione, an algicidal compound from the group of the diketopiperazines. Structurally this compound can be described as a cyclic dipeptide derived from glycine and proline (cyclo[Gly-Pro]). In contrast to isatin, which inhibits growth of the cyanobacteria *Microcystis aeruginosa* and *Synechococcus* sp., the diketopiperazine was only algicidal to *M. aeruginosa*, affecting cell wall integrity and intracellular structuring (Li *et al.* 2014b). Cyclo[Gly-Pro] was also isolated from a freshwater *Stenotrophomonas* sp. together with the algicide hydroquinone. Hydroquinone is also toxic to *M. aeruginosa* as well as *Synechococcus* sp. (Lin *et al.* 2016). This utilisation of structurally different algicides with at least overlapping host range is striking and might be a strategy to minimise resistance. Affected target organisms of the algicidal cyclo[Gly-Pro] were further studied by Li and co-workers after its isolation from a freshwater *Bacillus* species. Only four out of six cyanobacterial species tested were affected by this diketopiperazine (Li, Geng and Yang 2015). The co-isolated structurally related compound cyclo[Pro-Val] showed the same profile of algicidal activity as cyclo[Gly-Pro]. Recently, cyclo[Gly-Pro] has also been isolated from a marine *Bacillus* species and mechanistic studies showed that it inhibits photosynthetic activity and causes oxidative stress in the haptophyte *Phaeocystis globosa* (Tan *et al.* 2016). Other anti-cyanobacterial diketopiperazines include cyclo[Gly-Phe] isolated from a freshwater *Aeromonas* sp. (Guo *et al.* 2016b) as well as cyclo[Pro-Leu] and cyclo[4-OH-Pro-Leu] isolated from a freshwater Flavobacterium *Chryseobacterium* sp. (Guo *et al.* 2015). Despite their structural similarity, the latter two have distinct characteristics and act synergistically. Both algicides cause oxidative stress but cyclo[Pro-Leu] mainly inhibits antioxidases, while cyclo[4-OH-Pro-Leu] interrupts photosynthetic electron flux.

Amino-acid derivatives are among the most frequently identified algicides. Many studies use complex media based on peptone and yeast extract for bacterial cultivation. However, such media are not well suited for the purpose due to high background levels of amino-acid-derived metabolites. The surplus of amino-acid derivatives in the medium can mask low-abundant algicides due to insufficient chromatographic separation leading to false identifications. In addition, amino-acid derivatives might correctly be identified as algicidal but are not a product of the bacterium under study but rather a medium component. Consequently, special efforts have to be made to prove bacterial origin whenever complex media are used for cultivation.

Enzymes

The release of enzymes is closely associated with an algicidal lifestyle of bacteria (Smith *et al.* 1992; Martinez *et al.* 1996; Paul and Pohnert 2011; Lei *et al.* 2015; Li *et al.* 2016). Many algicidal enzymes belong to the hydrolases and might serve a dual function being algicidal as well as facilitating utilisation of host polymers by extracellular degradation. The hydrolases primarily target polymers of algal cell walls, which are easily accessible and vital for algal cellular integrity. An example is a marine *Pseudoalteromonas* species that produces two proteases that are algicidal to a diatom. One of the proteases is a serine protease and the other that has a 6-fold lower algicidal activity belongs to the metal proteases (Lee *et al.* 2000, 2002; Kohno *et al.* 2007). The activity is specific since another serine protease produced by the bacterium as well as several commercially available proteases did not exhibit algicidal activity. Substrate specificity and affinity to the target may be determining factors for the algicidal activity of proteases. The marine *K. algicida* also produces lytic proteases that can target diatoms. While four tested diatom species were lysed by the bacteria, one showed resistance in infection experiments. Closer inspection revealed an induced protease production by the algae that might be linked to a defence mechanism counteracting the enzymes from bacteria. In the resistant diatom, proteases are substantially upregulated in the presence of the lytic bacteria triggered by an as of yet unknown mechanism (Paul and Pohnert 2011, 2013). Apart from lytic activity, bacterial proteases can also affect cell motility. Excreted proteins from three Flavobacteria reduce motility of a dinoflagellate, and inhibition experiments indicated that these proteins are proteases (Mayali *et al.* 2008). However, the authors doubt that motility is the primary target of the protease but rather interpret the activity as a secondary effect of general toxicity. Algicidity has also been associated with the production of β-glucosidases by a marine *P. haloplanktis* strain with specific toxicity to the dinoflagellate *Prorocentrum* spp. without affecting other dinoflagellates (Kim *et al.* 2009a). Naturally associated bacteria in the phycosphere of the dinoflagellate *A. tamarense* also release carbohydrate-degrading enzymes directly causing the lysis of the alga (Wang *et al.* 2010). The potential target of β-glucosidases and other glycosidases is the cell wall. Activity of amylases, cellulases and xylanases in the marine bacterium *Flammeovirga yaeyamensis* (Bacteroidetes) has been linked to the degradation of algal cell walls as well (Chen, Bai and Chang 2013). Similarly, several cellulolytic marine bacteria isolated from mollusc gut negatively affect algal cell wall integrity (Munoz *et al.* 2014). A complex toxic mechanism has been elucidated for freshwater *C. prasina*. As discussed in the section Regulation, this mechanism involves chemotaxis to diatoms, attachment to the cells via flagella and subsequent enzymatic degradation of the cell wall assisted by chitinases (Li *et al.* 2016). An indirect algicidal mechanism is used by *Rheinheimera* sp. (Gammaproteobacteria) and the Flavobacterium *Aquimarina* sp. which produce L-amino acid oxidases (Chen, Lin and Sheu 2010; Chen, Sheu and Sheu 2011). The hydrogen peroxide production that happens concomitantly with the amino acid oxidation is responsible for the algicidal effect on green algae as well as on cyanobacteria.

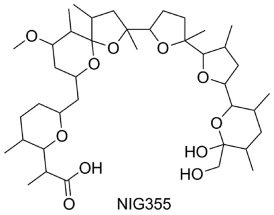

Figure 6. Algicidal polyketide.

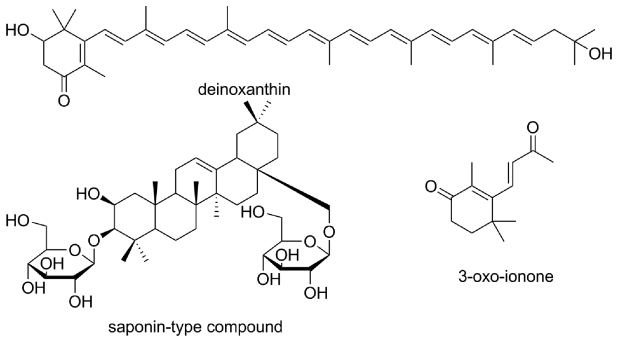

Figure 7. Algicidal terpenes.

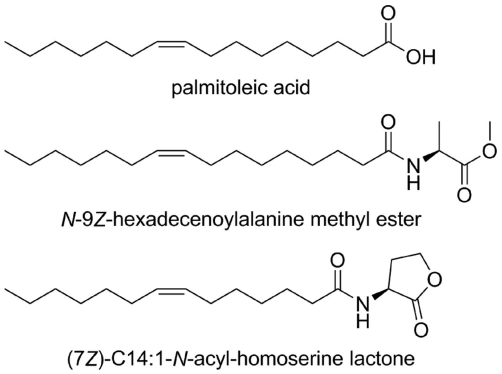

Figure 8. Algicidal fatty acid derivatives.

Polyketides

Despite the great variety of polyketides known, only one algicidal polyketides has been identified to date (Fig. 6). A polyether algicide was isolated from a mangrove sediment *St. malaysiensis* (Zheng *et al.* 2013). This polyether NIG355 is a stereoisomer of the known polyketide nigericin (Harvey *et al.* 2007). The isolated polyether inhibited growth of a haptophyte and a dinoflagellate but was less active against a green alga (Zheng *et al.* 2013). Although the authors did not comment on the mode of action, it can be hypothesised that it functions as an ionophore like nigericin does (Kevin, Meujo and Hamann 2009).

Terpenes

An algicidal terpene has been isolated from a freshwater *Deinococcus* sp. (Li *et al.* 2015). The algicide was identified as the red pigment deinoxanthin, which is acting on specific target organisms (Fig. 7). Only 5 out of 23 tested species of microalgae were susceptible and these belonged to different taxonomic groups, namely dinoflagellates, diatoms and haptophytes. The mechanism of action is not yet fully understood but the authors suggest the chromophore to facilitate ROS formation. This is in agreement with a measurable increase in ROS and subsequent loss of cellular integrity upon deinoxanthin treatment. Damage by ROS also seems to be involved in the anti-cyanobacterial activity of a triterpenoid saponin produced by a *Streptomyces* sp. isolated from soil (Luo *et al.* 2013). Another anti-cyanobacterial terpene derivative is a 3-oxo-ionone, which was isolated from a periphyton biofilm tentatively assigned by comparison with GC/MS libraries (Wu *et al.* 2011). Similar to the co-isolated indole, the terpene also affects photosynthesis.

Fatty acids and their derivatives

This small group of algicides covers simple fatty acids as well as more complex derivatives (Fig. 8). Although fatty acid derivatives are well known in algal allelopathic interactions (Legrand *et al.* 2003), they are rarely reported as bacterial algicides. A marine *Vibrio* sp. produces palmitoleic acid that inhibits growth of dinoflagellates (Li *et al.* 2014a) and to a minor extend of diatoms and a raphidophyte. Upon treatment with palmitoleic acid, impaired integrity of cell wall and membranes were visible prior to total cell lysis. A more complex algicide build from a fatty acid and an amino acid is *N*-9-hexadecenoylalanine methyl ester. This algicide was isolated from the two marine species *Loktanella koreensis* and *Roseovarius lutimaris* (Alphaproteobacteria), and inhibited growth of a diatom (Ziesche *et al.* 2015). Furthermore, *N*-acyl-homoserine-lactones produced by several marine bacteria from the *Roseobacter* clade have been identified as algicides (Ziesche *et al.* 2015).

Others

The two 2-pyrones 3-hexyl-4-hydroxyl-6-pentyl-2*H*-pyran-2-one and 3-hexyl-4-hydroxyl-6-heptyl-2*H*-pyran-2-one were isolated from a marine *Alteromonas* sp. (Cho 2012) (Fig. 9). Similar to the quinolones produced by this organism (see section Alkaloids), these pyrones are toxic to dinoflagellates and raphidophytes but less toxic to the green algae or haptophytes tested. The more lipophilic 3-hexyl-4-hydroxyl-6-heptyl-2*H*-pyran-2-one possesses higher algicidal activity a trend also described for other algicides, such as harmane. Benzoic acid isolated from a marine *Thalassospira* sp. (Alphaproteobacteria) is algicidal against the harmful dinoflagellate *Karenia mikimotoi* (Lu *et al.* 2016). As a potential mechanism of action, acidification of the cell leading to enzyme inhibition is discussed. Furthermore, a marine actinobacterial *Brevibacterium* sp. produces (2-isobutoxyphenyl)amine with toxicity to a dinoflagellate via degradation of membranes (An *et al.* 2015). A larger group of algicides produced by marine *P. gallaeciensis* are the roseobacticides (Seyedsayamdost *et al.* 2011a,b, 2014). The production of these algicides is triggered by algal breakdown products (see section Regulation). Potent algicidal activity of the roseobacticides with loss of cellular integrity and chloroplasts has been shown for a haptophyte; a cryptophyte and a diatom were also affected.

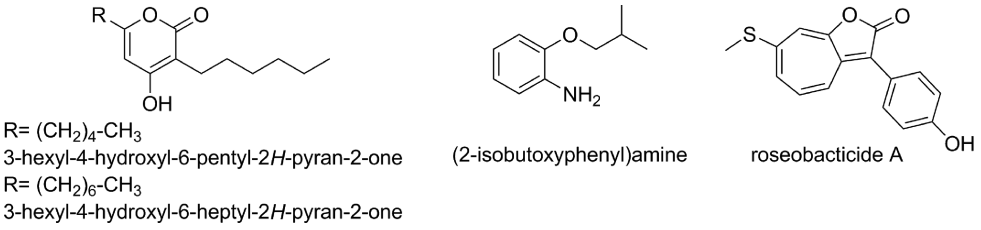

Figure 9. Algicidal metabolites of diverse biosynthetic origin. These metabolites cannot be unambiguously assigned to one of the compound classes in Figs 3 to 7.

Structures of algicides—general considerations

In conclusion, algicides are very versatile and possess a wide range of molecular targets. There is until now no way to predict activities since structurally similar algicides can address distinct targets while structurally diverse compounds result in similar phenotypic effects. Three algicidal modes of action have been shown for several algicides from different natural product classes and represent common algicidal principles: (i) the destruction of cell membranes and cell walls as structural features leading to loss of cellular integrity and lysis; (ii) the production of ROS leading to disturbance in redox homeostasis, radical reactions and consequently to loss of cellular functions; (iii) the impairment of photosynthesis depriving the cells of energy. These modes of action are not independent of each other since lipid peroxidation due to ROS disturbs membranes and ROS may damage photosynthetic pigments. Blocked photosynthesis, on the other hand, also facilitates the generation of ROS. Consequently, separating the true primary target from secondary effects is very challenging. Furthermore, there might be a bias since parameters such as ROS or photosynthetic activity are easily accessible with standard toolkits. The lack of other targets might be caused by a lack of suitable methods for their detection. Many studies thus remain in a descriptive state and do not report the primary targets of the algicides but merely secondary effects caused by cellular stress or dysregulation. Future research should go into detail with the identification of algicidal mechanisms using, for example, structure-activity tests, assays to identify molecular targets using standard biochemical methods or recent tools, such as activity-based protein profiling.

Ecological role of algicidal bacteria—the microbial loop

Based on the above considerations, we now want to summarise the general role of algicidal bacteria within the marine environment. Mostly in spring when nutrient levels are high, specific microalgae can become dominant in the surface ocean. Such algal blooms develop mainly under the influence of nutrient availability (nitrogen, phosphorus, silicate and iron) but microbial as well as grazing activity can also promote bloom termination. Phytoplankton blooms are highly productive, releasing up to 20% of the primary production as DOC into the ocean. Phytoplankton-derived organic matter is highly diverse and the complexity is even increased by bacterial metabolism (Kujawinski 2011). DOC bioavailability is tightly linked with bacterial growth and community composition (Wear *et al.* 2015). Bloom-associated bacteria can be assigned to the three major heterotrophic lineages Flavobacteria, Alphaproteobacteria (including *Roseobacter* spp.) and Gammaproteobacteria (Buchan *et al.* 2014), and distinct populations of bacteria are observed during the process of decomposition of the algal bloom (Teeling *et al.* 2012). A recent spatial-temporal study examining interactions of phytoplankton blooms and bacterioplankton community composition revealed that members of Bacteroidetes and Alphaproteobacteria dominated the bacterial community composition without being correlated to bloom-related variables. Less abundant bacterial phyla, on the other hand, were strongly associated with phytoplankton biomass or diatom:dinoflagellate ratio and showed high niche specificities (Bunse *et al.* 2016). DOM as sum parameter of all dissolved organic matter is thus not appropriately reflecting the influence of resource availability for bacteria. Uptake experiments using the specific substrates glucose, amino acids and ATP revealed preferences of Alpha- and Gammaproteobacteria as well as Bacteroidetes resulting in variable performance depending on the DOM fraction present. In contrast, Roseobacter as a dominant group that includes algicidal members were overrepresented on all substrates (Alonso-Sáez and Gasol 2007). In general, the microbial loop is dominated by bacteria utilising organic matter released by exudation, lysis and hydrolysis of phytoplankton (Azam *et al.* 1983; Bidle and Falkowski 2004). The entity of DOM generated by these processes is one of the largest pools of organic carbon globally. It might be recycled within the microbial loop or move to higher (grazing) or lower trophic levels (viruses) (Wilhelm and Suttle 2012). However, dominant processes also lead to its escape from the food web in form of inorganic gaseous carbon (CO_2, dimethylsulfide, etc.) or that it contributes to the ocean storage of non-degradable DOC in the deep sea known as the biological pump (Jiao *et al.* 2010; Buchan *et al.* 2014). Algicidal bacteria can actively modulate the carbon shuttling described above by arresting or inhibiting phytoplankton growth. More commonly, high lysis rates of phytoplankton populations triggered by algicidal bacteria will increase the abundance of DOM and POM (particulate organic matter) in the ocean (Mayali and Azam 2004; Roy and Chattopadhyay 2007). However, algicidal activity can also be very specific. Lysis of only one species or taxon can cause species shifts in the oceans' plankton without significantly affecting the overall photosynthetic activity (Kang *et al.* 2011). After lysis, resistant phytoplankton species and those creating temporary or resting stages might be responsible for the post-blooming shift in short-time phytoplankton diversity and also for longer lasting changes of dominance in the plankton (von Dassow and Montresor 2011). Especially specific bloom-terminating events by bacterial activity might substantially affect plankton composition (Sohn *et al.* 2004; Mayali, Franks and Azam 2008; Meyer *et al.* 2014). It can be argued that the frequency of such events might be substantial since especially high productive situations, as observed in algal blooms can nurture bacteria with algicidal effects (Bowen, Stolzenbach and Chisholm 1993). Solid data on the prevalence of algicidal effects in the field are however not available today—especially since methodological limitations of surveillance capacities as well as of analytical possibilities might lead to the bias towards contact or within-bloom interactions.

Conclusions and open questions

It becomes clear that algicidal bacteria and their lifestyles are highly diverse. This is also the case for the underlying regulative principles of alga–bacterium interactions. Multiple different mechanisms causing algicide activity and specificity have been identified in the last years, but often the true molecular targets or modes of action are not entirely understood. Some algicides seem to be rather species or taxa specific while others have a broader target spectrum, but no common patterns emerge, which again reflects the diversity. Mainly motivated by potential industrial applications many algicidal principles from small molecular weight secondary metabolites to enzymes have been identified. In most cases, however, the ecological function and concentrations of the algicides in the natural environment remain elusive. These active principles will now pave the way towards more elaborate studies involving *in situ* analytics as well as knock-out strategies to evaluate their true function in the interactions. It is fascinating to see that novel approaches in field work are already contributing to a better understanding of the role of algicidal bacteria within plankton communities. Especially the multiple regulations of alga–bacteria interactions contribute to our emerging understanding of interaction dynamics. Often novel insights also reveal additional layers of complexity. These become evident in micro- and mesocosm experiments, and it will be a major challenge to transfer the knowledge to field studies. Emerging possibilities in chemical analysis as well as transcriptomics will surely help to address the task. Even then, some more fundamental questions are still open, including the mechanisms of host specificity, or the identification of the true molecular targets of most algicides. In this context, the establishment of standard panels of microalgae for testing could be the task of an urgently needed initiative for standardisation. This is especially important since the emerging applications of algicidal bacteria in ecosystem engineering and biotechnology call for a reliable characterization of their activities before large-scale manipulations are envisaged.

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REFERENCES

Adachi M, Kanno T, Matsubara T *et al.* Promotion of cyst formation in the toxic dinoflagellate *Alexandrium* (Dinophyceae) by natural bacterial assemblages from Hiroshima Bay, Japan. *Mar Ecol Prog Ser* 1999;**191**:175–85.

Adolph S, Bach S, Blondel M *et al.* Cytotoxicity of diatom-derived oxylipins in organisms belonging to different phyla. *J Exp Biol* 2004;**207**:2935–46.

Alamri SA, Mohamed ZA. Selective inhibition of toxic cyanobacteria by beta-carboline-containing bacterium *Bacillus flexus* isolated from Saudi freshwaters. *Saudi J Biol Sci* 2013;**20**:357–63.

Alonso-Sáez L, Gasol JM. Seasonal variations in the contributions of different bacterial groups to the uptake of low-molecular-weight compounds in northwestern Mediterranean coastal waters. *Appl Environ Microb* 2007;**73**:3528–35.

Amaro AM, Fuentes MS, Ogalde SR *et al.* Identification and characterization of potentially algal-lytic marine bacteria strongly associated with the toxic dinoflagellate *Alexandrium catenella*. *J Eukaryot Microbiol* 2005;**52**:191–200.

Amin SA, Hmelo LR, van Tol HM *et al.* Interaction and signalling between a cosmopolitan phytoplankton and associated bacteria. *Nature* 2015;**522**:98–101.

Amin SA, Parker MS, Armbrust EV. Interactions between diatoms and bacteria. *Microbiol Mol Biol R* 2012;**76**:667–84.

An X, Zhang B, Zhang H *et al.* Discovery of an algicidal compound from *Brevibacterium* sp. BS01 and its effect on a harmful algal bloom-causing species, *Alexandrium tamarense*. *Front Microbiol* 2015;**6**:1235.

Anderson DM, Rengefors K. Community assembly and seasonal succession of marine dinoflagellates in a temperate estuary: the importance of life cycle events. *Limnol Oceanogr* 2006;**51**:860–73.

Aota Y, Nakajima H. Mutualistic relationships between phytoplankton and bacteria caused by carbon excretion from phytoplankton. *Ecol Res* 2001;**16**:289–99.

Armbrust EV. The life of diatoms in the world's oceans. *Nature* 2009;**459**:185–92.

Azam F, Fenchel T, Field JG *et al.* The ecological role of water-column microbes in the sea. *Mar Ecol Prog Ser* 1983;**10**:257–63.

Azam F, Malfatti F. Microbial structuring of marine ecosystems. *Nat Rev Microbiol* 2007;**5**:782–91.

Bai SJ, Huang LP, Su JQ *et al.* Algicidal effects of a novel marine actinomycete on the toxic dinoflagellate *Alexandrium tamarense*. *Curr Microbiol* 2011;**62**:1774–81.

Balestra C, Alonso-Saez L, Gasol JM *et al.* Group-specific effects on coastal bacterioplankton of polyunsaturated aldehydes produced by diatoms. *Aquatic Microb Ecol* 2011;**63**:123–31.

Balzano S, Corre E, Decelle J *et al.* Transcriptome analyses to investigate symbiotic relationships between marine protists. *Front Microbiol* 2015;**6**:98.

Banin E, Khare SK, Naider F *et al.* Proline-rich peptide from the coral pathogen *Vibrio shiloi* that inhibits photosynthesis of zooxanthellae. *Appl Environ Microb* 2001;**67**:1536–41.

Barbara GM, Mitchell JG. Bacterial tracking of motile algae. *FEMS Microbiol Ecol* 2003;**44**:79–87.

Barofsky A, Vidoudez C, Pohnert G. Metabolic profiling reveals growth stage variability in diatom exudates. *Limnol Oceanogr Meth* 2009;**7**:382–90.

Bassler BL. How bacteria talk to each other: regulation of gene expression by quorum sensing. *Curr Opinion Microbiol* 1999;**2**:582–7.

Behrenfeld MJ, O'Malley RT, Siegel DA *et al.* Climate-driven trends in contemporary ocean productivity. *Nature* 2006;**444**:752–5.

Bell W, Mitchell R. Chemotactic and growth responses of marine bacteria to algal extracellular products. *Biol Bull* 1972;**143**:265.

Berger M, Neumann A, Schulz S *et al.* Tropodithietic acid production in *Phaeobacter gallaeciensis* is regulated by N-acyl homoserine lactone-mediated quorum sensing. *J Bacteriol* 2011;**193**:6576–85.

Biddanda B, Benner R. Carbon, nitrogen, and carbohydrate fluxes during the production of particulate and dissolved organic matter by marine phytoplankton. *Limnol Oceanogr* 1997;**42**:506–18.

Bidle KD, Falkowski PG. Cell death in planktonic, photosynthetic microorganisms. *Nat Rev Microbiol* 2004;**2**:643–55.

Blée E. Impact of phyto-oxylipins in plant defense. *Trends Plant Sci* 2002;**7**:315–22.

Bowen JD, Stolzenbach KD, Chisholm SW. Simulating bacterial clustering around phytoplankton cells in a turbulent ocean. *Limnol Oceanogr* 1993;**38**:36–51.

Breckels MN, Boakes DE, Codling EA *et al*. Modelling the concentration of exuded dimethylsulphoniopropionate (DMSP) in the boundary layer surrounding phytoplankton cells. *J Plankton Res* 2010;**32**:253–7.

Breckels MN, Roberts EC, Archer SD *et al*. The role of dissolved infochemicals in mediating predator-prey interactions in the heterotrophic dinoflagellate *Oxyrrhis marina*. *J Plankton Res* 2011;**33**:629–39.

Buchan A, LeCleir GR, Gulvik CA *et al*. Master recyclers: features and functions of bacteria associated with phytoplankton blooms. *Nat Rev Microbiol* 2014;**12**:686–98.

Bunse C, Bertos-Fortis M, Sassenhagen I *et al*. Spatio-temporal interdependence of bacteria and phytoplankton during a Baltic Sea spring bloom. *Front Microbiol* 2016;**7**:517.

Cai GJ, Yang XJ, Lai QL *et al*. Lysing bloom-causing alga *Phaeocystis globosa* with microbial algicide: an efficient process that decreases the toxicity of algal exudates. *Sci Rep* 2016;**6**:11.

Chen CY, Bai MD, Chang JS. Improving microalgal oil collecting efficiency by pretreating the microalgal cell wall with destructive bacteria. *Biochem Eng J* 2013;**81**:170–6.

Chen WM, Lin CY, Sheu SY. Investigating antimicrobial activity in *Rheinheimera* sp. due to hydrogen peroxide generated by L-lysine oxidase activity. *Enzyme Microb Tech* 2010;**46**:487–93.

Chen WM, Sheu FS, Sheu SY. Novel L-amino acid oxidase with algicidal activity against toxic cyanobacterium *Microcystis aeruginosa* synthesized by a bacterium *Aquimarina* sp. *Enzyme Microb Tech* 2011;**49**:372–9.

Cherrier J, Valentine S, Hamill B *et al*. Light-mediated release of dissolved organic carbon by phytoplankton. *J Mar Syst* 2015;**147**:45–51.

Cho JY. Algicidal activity of marine *Alteromonas* sp. KNS-16 and isolation of active compounds. *Biosci Biotech Bioch* 2012;**76**:1452–8.

Cooper MB, Smith AG. Exploring mutualistic interactions between microalgae and bacteria in the omics age. *Curr Opin Plant Biol* 2015;**26**:147–53.

Cude W, Buchan A. Acyl-homoserine lactone-based quorum sensing in the Roseobacter clade: complex cell-to-cell communication controls multiple physiologies. *Front Microbiol* 2013;**4**:336.

Cude WN, Mooney J, Tavanaei AA *et al*. Production of the antimicrobial secondary metabolite indigoidine contributes to competitive surface colonization by the marine *Roseobacter Phaeobacter* sp. *Strain Y4I. Appl Environ Microb* 2012;**78**:4771–80.

Dahms HU, Ying X, Pfeiffer C. Antifouling potential of cyanobacteria: a mini-review. *Biofouling* 2006;**22**:317–27.

Dang H, Lovell CR. Microbial surface colonization and biofilm development in marine environments. *Microbiol Mol Biol R* 2016;**80**:91–138.

Dann LM, Paterson JS, Newton K *et al*. Distributions of virus-like particles and prokaryotes within microenvironments. *PLoS One* 2016;**11**:e0146984.

DeLong EF, Franks DG, Alldredge AL. Phylogenetic diversity of aggregate-attached vs. free-living marine bacterial assemblages. *Limnol Oceanogr* 1993;**38**:924–34.

Demuez M, Gonzalez-Fernandez C, Ballesteros M. Algicidal microorganisms and secreted algicides: new tools to induce microalgal cell disruption. *Biotechnol Adv* 2015a;**33**:1615–25.

Demuez M, Mahdy A, Tomás-Pejó E *et al*. Enzymatic cell disruption of microalgae biomass in biorefinery processes. *Biotechnol Bioeng* 2015b;**112**:1955–66.

Deng Y, Wu JE, Eberl L *et al*. Structural and functional characterization of diffusible signal factor family quorum-sensing signals produced by members of the *Burkholderia cepacia* complex. *Appl Environ Microb* 2010;**76**:4675–83.

Desbois AP, Mearns-Spragg A, Smith VJ. A fatty acid from the diatom *Phaeodactylum tricornutum* is antibacterial against diverse bacteria including multi-resistant *Staphylococcus aureus* (MRSA). *Mar Biotechnol* 2009;**11**:45–52.

Diggle SP, Matthijs S, Wright VJ *et al*. The *Pseudomonas aeruginosa* 4-quinolone signal molecules HHQ and PQS play multifunctional roles in quorum sensing and iron entrapment. *Chem Biol* 2007;**14**:87–96.

Doubell MJ, Prairie JC, Yamazaki H. Millimeter scale profiles of chlorophyll fluorescence: Deciphering the microscale spatial structure of phytoplankton. *Deep Sea Res Pt II* 2014;**101**:207–15.

Dubern J-F, Diggle SP. Quorum sensing by 2-alkyl-4-quinolones in *Pseudomonas aeruginosa* and other bacterial species. *Mol BioSyst* 2008;**4**:882–8.

Dutz J, Breteler W, Kramer G. Inhibition of copepod feeding by exudates and transparent exopolymer particles (TEP) derived from a *Phaeocystis globosa* dominated phytoplankton community. *Harmful Algae* 2005;**4**:929–40.

Fuqua C, Greenberg EP. Listening in on bacteria: acyl-homoserine lactone signalling. *Nat Rev Mol Cell Bio* 2002;**3**:685–95.

Geng H, Belas R. Molecular mechanisms underlying roseobacter-phytoplankton symbioses. *Curr Opin Biotechnol* 2010;**21**:332–8.

Gerphagnon M, Macarthur DJ, Latour D *et al*. Microbial players involved in the decline of filamentous and colonial cyanobacterial blooms with a focus on fungal parasitism. *Environ Microbiol* 2015;**17**:2573–87.

Goecke F, Labes A, Wiese J *et al*. Chemical interactions between marine macroalgae and bacteria. *Mar Ecol Prog Ser* 2010;**409**:267–99.

Goecke F, Thiel V, Wiese J *et al*. Algae as an important environment for bacteria – phylogenetic relationships among new bacterial species isolated from algae. *Phycologia* 2013;**52**:14–24.

Grandclement C, Tannieres M, Morera S *et al*. Quorum quenching: role in nature and applied developments. *Fems Microbiol Rev* 2016;**40**:86–116.

Grossart HP. Ecological consequences of bacterioplankton lifestyles: changes in concepts are needed. *Environ Microbiol Rep* 2010;**2**:706–14.

Grossart HP, Levold F, Allgaier M *et al*. Marine diatom species harbour distinct bacterial communities. *Environ Microbiol* 2005;**7**:860–73.

Grosser K, Zedler L, Schmitt M *et al*. Disruption-free imaging by Raman spectroscopy reveals a chemical sphere with antifouling metabolites around macroalgae. *Biofouling* 2012;**28**:687–96.

Gumbo RJ, Ross G, Cloete ET. Biological control of *Microcystis* dominated harmful algal blooms. *Afr J Biotechnol* 2008;**7**:4765–73.

Guo R, Wang H, Suh YS *et al*. Transcriptomic profiles reveal the genome-wide responses of the harmful dinoflagellate *Cochlodinium polykrikoides* when exposed to the algicide copper sulfate. *BMC Genomics* 2016a;**17**:29.

Guo X, Liu X, Wu L *et al*. The algicidal activity of *Aeromonas* sp. strain GLY-2107 against bloom-forming *Microcystis aeruginosa* is regulated by N-acyl homoserine lactone-mediated quorum sensing. *Environ Microbiol* 2016b;**18**:3867–83.

Guo XL, Liu XL, Pan JL *et al*. Synergistic algicidal effect and mechanism of two diketopiperazines produced by

Chryseobacterium sp. strain GLY-1106 on the harmful bloom-forming *Microcystis aeruginosa*. *Sci Rep* 2015;**5**.

Hansell DA, Carlson CA, Repeta DJ *et al*. Dissolved organic matter in the ocean a controversy stimulates new insights. *Oceanography* 2009;**22**:202–11.

Harvey BM, Mironenko T, Sun YH *et al*. Insights into polyether biosynthesis from analysis of the nigericin biosynthetic gene cluster in *Streptomyces* sp. DSM4137. *Chem Biol* 2007;**14**:703–14.

Harvey EL, Deering RW, Rowley DC *et al*. A bacterial quorum-sensing precursor induces mortality in the marine coccolithophore, Emiliania huxleyi. *Front Microbiol* 2016;**7**:59.

Hasegawa Y, Martin JL, Giewat MW *et al*. Microbial community diversity in the phycosphere of natural populations of the toxic alga, Alexandrium fundyense. *Environ Microbiol* 2007;**9**:3108–21.

Hibayashi R, Imamura N. Action mechanism of a selective anti-cyanobacterial compound, argimicin A. *J Antibiot* 2003;**56**:154–9.

Hibbing ME, Fuqua C, Parsek MR *et al*. Bacterial competition: surviving and thriving in the microbial jungle. *Nat Rev Microbiol* 2010;**8**:15–25.

Holmstrom C, Kjelleberg S. Marine *Pseudoalteromonas* species are associated with higher organisms and produce biologically active extracellular agents. *FEMS Microbiol Ecol* 1999;**30**:285–93.

Hu L, Peng X, Zhou J *et al*. Characterizing the interactions among a dinoflagellate, flagellate and bacteria in the phycosphere of *Alexandrium tamarense* (Dinophyta). *Front Mar Sci* 2015;**2**, https://doi.org/10.3389/fmars.2015.00100.

Hunt DE, David LA, Gevers D *et al*. Resource partitioning and sympatric differentiation among closely related bacterioplankton. *Science* 2008;**320**:1081–5.

Imai I, Ishida Y, Hata Y. Killing of marine phytoplankton by a gliding bacterium *Cytophaga* sp., isolated from the coastal sea of Japan. *Mar Biol* 1993;**116**:527–32.

Imai I, Sunahara T, Nishikawa T *et al*. Fluctuations of the red tide flagellates *Chattonella* spp. (Raphidophyceae) and the algicidal bacterium *Cytophaga* sp. in the Seto Inland Sea, Japan. *Mar Biol* 2001;**138**:1043–9.

Imamura N, Motoike I, Noda M *et al*. Argimicin A, a novel anti-cyanobacterial compound produced by an algae-lysing bacterium. *J Antibiot* 2000;**53**:1317–9.

Jancula D, Marsalek B. Critical review of actually available chemical compounds for prevention and management of cyanobacterial blooms. *Chemosphere* 2011;**85**:1415–22.

Jasti S, Sieracki ME, Poulton NJ *et al*. Phylogenetic diversity and specificity of bacteria closely associated with *Alexandrium* spp. and other phytoplankton. *Appl Environ Microb* 2005;**71**:3483–94.

Jeong H, Yim JH, Lee C *et al*. Genomic blueprint of *Hahella chejuensis*, a marine microbe producing an algicidal agent. *Nucleic Acids Res* 2005;**33**:7066–73.

Jeong SY, Ishida K, Ito Y *et al*. Bacillamide, a novel algicide from the marine bacterium, *Bacillus* sp. SY-1, against the harmful dinoflagellate, *Cochlodinium polykrikoides*. *Tetrahedron Lett* 2003;**44**:8005–7.

Jiao N, Herndl GJ, Hansell DA *et al*. Microbial production of recalcitrant dissolved organic matter: long-term carbon storage in the global ocean. *Nat Rev Microbiol* 2010;**8**:593–9.

Jung SW, Kim BH, Katano T *et al*. *Pseudomonas fluorescens* HYK0210-SK09 offers species-specific biological control of winter algal blooms caused by freshwater diatom *Stephanodiscus hantzschii*. *J Appl Microbiol* 2008;**105**:186–95.

Kang YH, Jung SW, Jo SH *et al*. Field assessment of the potential of algicidal bacteria against diatom blooms. *Biocontrol Sci Techn* 2011;**21**:969–84.

Keeling PJ, Burki F, Wilcox HM *et al*. The Marine Microbial Eukaryote Transcriptome Sequencing Project (MMETSP): illuminating the functional diversity of eukaryotic life in the oceans through transcriptome sequencing. *PLoS Biol* 2014;**12**:e1001889.

Keller L, Surette MG. Communication in bacteria: an ecological and evolutionary perspective. *Nat Rev Microbiol* 2006;**4**:249–58.

Kevin DA, Meujo DAF, Hamann MT. Polyether ionophores: broad-spectrum and promising biologically active molecules for the control of drug-resistant bacteria and parasites. *Expert Opin Drug Dis* 2009;**4**:109–46.

Kim D, Kim JF, Yim JH *et al*. Red to red - the marine bacterium *Hahella chejuensis* and its product prodigiosin for mitigation of harmful algal blooms. *J Microbiol Biotechn* 2008;**18**:1621–9.

Kim D, Park YK, Lee JS *et al*. Analysis of a prodigiosin biosynthetic gene cluster from the marine bacterium *Hahella chejuensis* KCTC 2396. *J Microbiol Biotechn* 2006;**16**:1912–8.

Kim JD, Kim JY, Park JK *et al*. Selective control of the *Prorocentrum minimum* harmful algal blooms by a novel algal-lytic bacterium *Pseudoalteromonas haloplanktis* AFMB-008041. *Mar Biotechnol* 2009a;**11**:463–72.

Kim YS, Lee D-S, Jeong S-Y *et al*. Isolation and characterization of a marine algicidal bacterium against the harmful raphidophyceae *Chattonella marina*. *J Microbiol* 2009b;**47**:9–18.

Kim YS, Son HJ, Jeong SY. Isolation of an algicide from a marine bacterium and its effects against the toxic dinoflagellate *Alexandrium catenella* and other harmful algal bloom species. *J Microbiol* 2015;**53**:511–7.

Kirchman DL. The ecology of Cytophaga-Flavobacteria in aquatic environments. *FEMS Microbiol Ecol* 2002;**39**:91–100.

Kodani S, Imoto A, Mitsutani A *et al*. Isolation and identification of the antialgal compound, harmane (1-methyl-beta-carboline), produced by the algicidal bacterium, *Pseudomonas* sp. K44-1. *J Appl Phycol* 2002;**14**:109–14.

Kohno D, Sakiyama Y, Lee S-O *et al*. Cloning and characterization of a gene encoding algicidal serine protease from *Pseudoalteromonas* sp. strain A28. *J Environ Biotech* 2007;**7**:99–102.

Kouzuma A, Watanabe K. Exploring the potential of algae/bacteria interactions. *Curr Opin Biotechnol* 2015;**33**:125–9.

Kujawinski EB. The impact of microbial metabolism on marine dissolved organic matter. *Ann Rev Mar Sci* 2011;**3**:567–99.

Kurth C, Schieferdecker S, Athanasopoulou K *et al*. Variochelins, lipopeptide siderophores from *Variovorax boronicumulans* discovered by genome mining. *J Nat Prod* 2016;**79**:865–72.

Lee SO, Kato J, Nakashima K *et al*. Cloning and characterization of extracellular metal protease gene of the algicidal marine bacterium *Pseudoalteromonas* sp. strain A28. *Biosci Biotech Bioch* 2002;**66**:1366–9.

Lee SO, Kato J, Takiguchi N *et al*. Involvement of an extracellular protease in algicidal activity of the marine bacterium *Pseudoalteromonas* sp. strain A28. *Appl Environ Microb* 2000;**66**:4334–9.

Leflaive J, Ten-Hage L. Algal and cyanobacterial secondary metabolites in freshwaters: a comparison of allelopathic compounds and toxins. *Freshwater Biol* 2007;**52**:199–214.

Legrand C, Rengefors K, Fistarol GO *et al*. Allelopathy in phytoplankton - biochemical, ecological and evolutionary aspects. *Phycologia* 2003;**42**:406–19.

Lei XQ, Li D, Li Y *et al.* Comprehensive insights into the response of *Alexandrium tamarense* to algicidal component secreted by a marine bacterium. *Front Microbiol* 2015;**6**:7.

Lenneman EM, Wang P, Barney BM. Potential application of algicidal bacteria for improved lipid recovery with specific algae. *FEMS Microbiol Lett* 2014;**354**:102–10.

Lewis SM, Corpe WA. Prodigiosin-producing bacteria from marine sources. *Appl Microbiol* 1964;**12**:13–7.

Li D, Zhang HJ, Fu LJ *et al.* A novel algicide: evidence of the effect of a fatty acid compound from the marine bacterium, *Vibrio* sp. BS02 on the harmful dinoflagellate, *Alexandrium tamarense*. *PLoS One* 2014a;**9**:e91201.

Li Y, Lei X, Zhu H *et al.* Chitinase producing bacteria with direct algicidal activity on marine diatoms. *Sci Rep* 2016;**6**:21984.

Li Y, Zhu H, Lei X *et al.* The first evidence of deinoxanthin from *Deinococcus* sp. Y35 with strong algicidal effect on the toxic dinoflagellate *Alexandrium tamarense*. *J Hazard Mater* 2015;**290**:87–95.

Li Z, Lin S, Liu X *et al.* A freshwater bacterial strain, *Shewanella* sp. Lzh-2, isolated from Lake Taihu and its two algicidal active substances, hexahydropyrrolo[1,2-a]pyrazine-1,4-dione and 2,3-indolinedione. *Appl Microbiol Biot* 2014b;**98**:4737–48.

Li ZH, Geng MX, Yang H. Algicidal activity of *Bacillus* sp. Lzh-5 and its algicidal compounds against *Microcystis aeruginosa*. *Appl Microbiol Biot* 2015;**99**:981–90.

Lin S, Geng M, Liu X *et al.* On the control of *Microcystis aeruginosa* and *Synechococccus* species using an algicidal bacterium, *Stenotrophomonas* F6, and its algicidal compounds cyclo-(Gly-Pro) and hydroquinone. *J Appl Phycol* 2016;**28**:345–55.

Liu ZZ, Zhu JP, Li M *et al.* Effects of freshwater bacterial siderophore on *Microcystis and* Anabaena. *Biol Control* 2014;**78**:42–8.

Long RA, Qureshi A, Faulkner DJ *et al.* 2-n-pentyl-4-quinolinol produced by a marine *Alteromonas* sp. and its potential ecological and biogeochemical roles. *Appl Environ Microb* 2003;**69**:568–76.

Lu X, Zhou B, Xu L *et al.* A marine algicidal *Thalassospira* and its active substance against the harmful algal bloom species *Karenia mikimotoi*. *Appl Microbiol Biot* 2016;**100**: 5131–9.

Luo J, Wang Y, Tang S *et al.* Isolation and identification of algicidal compound from *Streptomyces* and algicidal mechanism to *Microcystis aeruginosa*. *PLoS One* 2013;**8**:e76444.

McCarren J, Becker JW, Repeta DJ *et al.* Microbial community transcriptomes reveal microbes and metabolic pathways associated with dissolved organic matter turnover in the sea. *P Natl Acad Sci USA* 2010;**107**:16420–7.

Manefield M, Rasmussen TB, Henzter M *et al.* Halogenated furanones inhibit quorum sensing through accelerated LuxR turnover. *Microbiology* 2002;**148**:1119–27.

Martinez J, Smith DC, Steward GF *et al.* Variability in ectohydrolytic enzyme activities of pelagic marine bacteria and its significance for substrate processing in the sea. *Aquat Microb Ecol* 1996;**10**:223–30.

Martiny JBH, Riemann L, Marston MF *et al.* Antagonistic coevolution of marine planktonic viruses and their hosts. In: Carlson CA, Giovannoni SJ (eds.) *Annual Review of Marine Science. Vol 6*. Palo Alto: Annual Reviews, 2014:393–414.

Mashburn-Warren L, Howe J, Garidel P *et al.* Interaction of quorum signals with outer membrane lipids: insights into prokaryotic membrane vesicle formation. *Mol Microbiol* 2008;**69**:491–502.

Mayali X, Azam F. Algicidal bacteria in the sea and their impact on algal blooms. *J Eukaryot Microbiol* 2004;**51**:139–44.

Mayali X, Doucette GJ. Microbial community interactions and population dynamics of an algicidal bacterium active against *Karenia brevis* (Dinophyceae). *Harmful Algae* 2002;**1**:277–93.

Mayali X, Franks PJS, Azam F. Cultivation and ecosystem role of a marine *Roseobacter* clade-affiliated cluster bacterium. *Appl Environ Microb* 2008;**74**:2595–603.

Mayali X, Franks PJS, Tanaka Y *et al.* Bacteria-induced motility reduction in *Lingulodinium polyedrum* (Dinophyceae). *J Phycol* 2008;**44**:923–8.

Mayali X, Weber PK, Mabery S *et al.* Phylogenetic patterns in the microbial response to resource availability: amino acid incorporation in San Francisco Bay. *PLoS One* 2014;**9**:e95842.

Mertens KN, Rengefors K, Moestrup O *et al.* A review of recent freshwater dinoflagellate cysts: taxonomy, phylogeny, ecology and palaeocology. *Phycologia* 2012;**51**:612–9.

Meyer KA, O'Neil JM, Hitchcock GL *et al.* Microbial production along the West Florida Shelf: Responses of bacteria and viruses to the presence and phase of Karenia brevis blooms. *Harmful Algae* 2014;**38**:110–8.

Michalak I, Chojnacka K. Algae as production systems of bioactive compounds. *Eng Life Sci* 2015;**15**:160–76.

Moustafa A, Evans AN, Kulis DM *et al.* Transcriptome profiling of a toxic dinoflagellate reveals a gene-rich protist and a potential impact on gene expression due to bacterial presence. *PLoS One* 2010;**5**:e9688.

Mu R-M, Fan Z-Q, Pei H-Y *et al.* Isolation and algae-lysing characteristics of the algicidal bacterium B5. *J Environ Sci (China)* 2007;**19**:1336–40.

Munoz C, Hidalgo C, Zapata M *et al.* Use of cellulolytic marine bacteria for enzymatic pretreatment in microalgal biogas production. *Appl Environ Microb* 2014;**80**:4199–206.

Nakashima T, Kim D, Miyazaki Y *et al.* Mode of action of an antialgal agent produced by a marine gammaproteobacterium against *Chattonella marina*. *Aquat Microb Ecol* 2006a;**45**:255–62.

Nakashima T, Miyazaki Y, Matsuyama Y *et al.* Producing mechanism of an algicidal compound against red tide phytoplankton in a marine γ-proteobacterium. *Appl Microbiol Biot* 2006b;**73**:684–90.

Natrah FMI, Bossier P, Sorgeloos P *et al.* Significance of microalgal-bacterial interactions for aquaculture. *Rev Aquacult* 2014;**6**:48–61.

Natrah FMI, Kenmegne MM, Wiyoto W *et al.* Effects of microalgae commonly used in aquaculture on acyl-homoserine lactone quorum sensing. *Aquaculture* 2011;**317**:53–7.

Nealson KH, Hastings JW. Bacterial bioluminescence: its control and ecological significance. *Microbiol Rev* 1979;**43**:496–518.

Nissimov J, Rosenberg E, Munn CB. Antimicrobial properties of resident coral mucus bacteria of Oculina patagonica. *FEMS Microbiol Lett* 2009;**292**:210–5.

Park J-H, Yoshinaga I, Nishikawa T *et al.* Algicidal bacteria in particle-associated form and in free-living form during a diatom bloom in the Seto Inland Sea, Japan. *Aquat Microb Ecol* 2010;**60**:151–61.

Paul C, Mausz MA, Pohnert G. A co-culturing/metabolomics approach to investigate chemically mediated interactions of planktonic organisms reveals influence of bacteria on diatom metabolism. *Metabolomics* 2013;**9**:349–59.

Paul C, Pohnert G. Interactions of the algicidal bacterium *Kordia algicida* with diatoms: regulated protease excretion for specific algal lysis. *PLoS One* 2011;**6**:e21032.

Paul C, Pohnert G. Induction of protease release of the resistant diatom *Chaetoceros didymus* in response to lytic enzymes from an algicidal bacterium. *PLoS One* 2013;**8**: e57577.

Pesci EC, Milbank JBJ, Pearson JP *et al*. Quinolone signaling in the cell-to-cell communication system of Pseudomonas aeruginosa. *P Natl Acad Sci USA* 1999;**96**:11229–34.

Pinhassi J, Sala MM, Havskum H *et al*. Changes in bacterioplankton composition under different phytoplankton regimens. *Appl Environ Microb* 2004;**70**:6753–66.

Pokrzywinski KL, Place AR, Warner ME *et al*. Investigation of the algicidal exudate produced by *Shewanella* sp. IRI-160 and its effect on dinoflagellates. *Harmful Algae* 2012;**19**:23–9.

Prince EK, Pohnert G. Searching for signals in the noise: metabolomics in chemical ecology. *Anal Bioanal Chem* 2010;**396**:193–7.

Rajamani S, Bauer WD, Robinson JB *et al*. The vitamin riboflavin and its derivative lumichrome activate the LasR bacterial quorum-sensing receptor. *Mol Plant-Microbe In* 2008;**21**:1184–92.

Rajamani S, Teplitski M, Kumar A *et al*. N-Acyl homoserine lactone lactonase inactivation of quorum sinsings agonists produced by *Chlamydomonas reinhardtii* (Chlorophyta) and characterization of transgenic algae. *J Phycol* 2011;**47**:1219–27.

Ramanan R, Kim B-H, Cho D-H *et al*. Algae-bacteria interactions: evolution, ecology and emerging applications. *Biotechnol Adv* 2016;**34**:14–29.

Rao D, Webb JS, Kjelleberg S. Microbial colonization and competition on the marine alga *Ulva australis*. *Appl Environ Microb* 2006;**72**:5547–55.

Ray S, Bagchi SN. Nutrients and pH regulate algicide accumulation in cultures of the cyanobacterium *Oscillatoria laetevirens*. *New Phytol* 2001;**149**:455–60.

Ribalet F, Intertaglia L, Lebaron P *et al*. Differential effect of three polyunsaturated aldehydes on marine bacterial isolates. *Aquat Toxicol* 2008;**86**:249–55.

Rohwer F, Thurber RV. Viruses manipulate the marine environment. *Nature* 2009;**459**:207–12.

Rolland JL, Stien D, Sanchez-Ferandin S *et al*. Quorum sensing and quorum quenching in the phycosphere of phytoplankton: a case of chemical interactions in ecology. *J Chem Ecol* 2016;**42**:1201–11.

Romero M, Diggle SP, Heeb S *et al*. Quorum quenching activity in *Anabaena* sp. PCC 7120: identification of AiiC, a novel AHL-acylase. *FEMS Microbiol Lett* 2008;**280**:73–80.

Romero M, Martin-Cuadrado A-B, Otero A. Determination of whether quorum quenching is a common activity in marine bacteria by analysis of cultivable bacteria and metagenomic sequences. *Appl Environ Microb* 2012;**78**:6345–8.

Romero M, Martin-Cuadrado AB, Roca-Rivada A *et al*. Quorum quenching in cultivable bacteria from dense marine coastal microbial communities. *FEMS Microbiol Ecol* 2011;**75**:205–17.

Roth PB, Twiner MJ, Mikulski CM *et al*. Comparative analysis of two algicidal bacteria active against the red tide dinoflagellate *Karenia brevis*. *Harmful Algae* 2008;**7**:682–91.

Roy S, Chattopadhyay J. Towards a resolution of 'the paradox of the plankton': A brief overview of the proposed mechanisms. *Ecol Complex* 2007;**4**:26–33.

Ruff SE, Probandt D, Zinkann AC *et al*. Indications for algae-degrading benthic microbial communities in deep-sea sediments along the Antarctic Polar Front. *Deep Sea Res Pt II* 2014;**108**:6–16.

Safari M, Amache R, Esmaeilishirazifard E *et al*. Microbial metabolism of quorum-sensing molecules acyl-homoserine lactones, gamma-heptalactone and other lactones. *Appl Microbiol Biot* 2014;**98**:3401–12.

Saha M, Rempt M, Stratil SB *et al*. Defence chemistry modulation by light and temperature shifts and the resulting effects on associated epibacteria of *Fucus vesiculosus*. *PLoS One* 2014;**9**:e105333.

Sakata T, del Castillo CS, Yoshikawa T *et al*. Chemical structures of quinolinol compounds produced by marine *Pseudoalteromonas* sp. A1-J11. *Mem Fac Fish Kagoshima Univ* 2008;**57**:29–35.

Sakata T, Yoshikawa T, Nishitarumizu S. Algicidal activity and identification of an algicidal substance produced by marine *Pseudomonas* sp. C55a-2. *Fish Sci* 2011;**77**:397–402.

Sapp M, Schwaderer AS, Wiltshire KH *et al*. Species-specific bacterial communities in the phycosphere of microalgae? *Microb Ecol* 2007;**53**:683–99.

Sarmento H, Gasol JM. Use of phytoplankton-derived dissolved organic carbon by different types of bacterioplankton. *Environ Microbiol* 2012;**14**:2348–60.

Sawabe T, Makino H, Tatsumi M *et al*. *Pseudoalteromonas bacteriolytica* sp. nov., a marine bacterium that is the causative agent of red spot disease of *Laminaria japonica*. *Int J Syst Bacteriol* 1998;**48**:769–74.

Segev E, Wyche TP, Kim KH *et al*. Dynamic metabolic exchange governs a marine algal-bacterial interaction. *eLife* 2016;**5**:28.

Seong KA, Jeong HJ. Interactions between marine bacteria and red tide organisms in Korean waters. *Algae* 2013;**28**:297–305.

Seyedsayamdost MR, Carr G, Kolter R *et al*. Roseobacticides: Small molecule modulators of an algal-bacterial symbiosis. *J Am Chem Soc* 2011a;**133**:18343–9.

Seyedsayamdost MR, Case RJ, Kolter R *et al*. The Jekyll-and-Hyde chemistry of *Phaeobacter gallaeciensis*. *Nat Chem* 2011b;**3**:331–5.

Seyedsayamdost MR, Wang RR, Kolter R *et al*. Hybrid biosynthesis of roseobacticides from algal and bacterial precursor molecules. *J Am Chem Soc* 2014;**136**:15150–3.

Seymour JR, Ahmed T, Stocker R. Bacterial chemotaxis towards the extracellular products of the toxic phytoplankton *Heterosigma akashiwo*. *J Plankton Res* 2009;**31**:1557–61.

Shao JH, Li RH, Lepo JE *et al*. Potential for control of harmful cyanobacterial blooms using biologically derived substances: problems and prospects. *J Environ Manage* 2013;**125**:149–55.

Shi M, Zou L, Liu XY *et al*. A novel bacterium *Saprospira* sp. strain PdY3 forms bundles and lyses cyanobacteria. *Front Biosci* 2006;**11**:1916–23.

Shieh WY, Chen YW, Chaw SM *et al*. *Vibrio ruber* sp. nov., a red, facultatively anaerobic, marine bacterium isolated from sea water. *Int J Syst Evol Microbiol* 2003;**53**:479–84.

Skerratt JH, Bowman JP, Hallegraeff G *et al*. Algicidal bacteria associated with blooms of a toxic dinoflagellate in a temperate Australian estuary. *Mar Ecol Prog Ser* 2002;**244**:1–15.

Slightom RN, Buchan A. Surface colonization by marine roseobacters: integrating genotype and phenotype. *Appl Environ Microb* 2009;**75**:6027–37.

Smith DC, Simon M, Alldredge AL *et al*. Intense hydrolytic enzyme activity on marine aggregates and implications for rapid particle dissolution. *Nature* 1992;**359**:139–42.

Smriga S, Fernandez VI, Mitchell JG *et al*. Chemotaxis toward phytoplankton drives organic matter partitioning among marine bacteria. *P Natl Acad Sci USA* 2016;**113**:1576–81.

Sohn JH, Lee JH, Yi H *et al*. *Kordia algicida* gen. nov., sp nov., an algicidal bacterium isolated from red tide. *Int J Syst Evol Micr* 2004;**54**:675–80.

Sonnenschein EC, Syit DA, Grossart HP *et al*. Chemotaxis of *Marinobacter adhaerens* and its impact on attachment to the diatom *Thalassiosira weissflogii*. *Appl Environ Microb* 2012;**78**:6900–7.

Strmecki S, Plavsic M, Steigenberger S *et al.* Characterization of phytoplankton exudates and carbohydrates in relation to their complexation of copper, cadmium and iron. *Mar Ecol Prog Ser* 2010;**408**:33–46.

Sule P, Belas R. A novel inducer of *Roseobacter* motility is also a disruptor of algal symbiosis. *J Bacteriol* 2013;**195**:637–46.

Syrpas M, Ruysbergh E, Blommaert L *et al.* Haloperoxidase mediated quorum quenching by Nitzschia cf pellucida: study of the metabolization of N-acyl homoserine lactones by a benthic diatom. *Mar Drugs* 2014;**12**:352–67.

Tan S, Hu X, Yin P *et al.* Photosynthetic inhibition and oxidative stress to the toxic *Phaeocystis globosa* caused by a diketopiperazine isolated from products of algicidal bacterium metabolism. *J Microbiol* 2016;**54**:364–75.

Teeling H, Fuchs BM, Becher D *et al.* Substrate-controlled succession of marine bacterioplankton populations induced by a phytoplankton bloom. *Science* 2012;**336**:608–11.

Teeling H, Fuchs BM, Bennke CM *et al.* Recurring patterns in bacterioplankton dynamics during coastal spring algae blooms. *eLife* 2016;**5**:e11888.

Teplitski M, Chen HC, Rajamani S *et al.* *Chlamydomonas reinhardtii* secretes compounds that mimic bacterial signals and interfere with quorum sensing regulation in bacteria. *Plant Physiol* 2004;**134**:137–46.

Thomson NR, Crow MA, McGowan SJ *et al.* Biosynthesis of carbapenem antibiotic and prodigiosin pigment in *Serratia* is under quorum sensing control. *Mol Microbiol* 2000;**36**:539–56.

Tilney CL, Pokrzywinski KL, Coyne KJ *et al.* Effects of a bacterial algicide, IRI-160AA, on dinoflagellates and the microbial community in microcosm experiments. *Harmful Algae* 2014a;**39**:210–22.

Tilney CL, Pokrzywinski KL, Coyne KJ *et al.* Growth, death, and photobiology of dinoflagellates (Dinophyceae) under bacterial-algicide control. *J Appl Phycol* 2014b;**26**:2117–27.

Tomaru Y, Shirai Y, Nagasaki K. Ecology, physiology and genetics of a phycodnavirus infecting the noxious bloom-forming raphidophyte *Heterosigma akashiwo*. *Fish Sci* 2008;**74**:701–11.

Van Donk E. Chemical information transfer in freshwater plankton. *Ecol Inform* 2007;**2**:112–20.

Van Wichelen J, Vanormelingen P, Codd GA *et al.* The common bloom-forming cyanobacterium *Microcystis* is prone to a wide array of microbial antagonists. *Harmful Algae* 2016;**55**:97–111.

Vanelslander B, Paul C, Grueneberg J *et al.* Daily bursts of biogenic cyanogen bromide (BrCN) control biofilm formation around a marine benthic diatom. *P Natl Acad Sci USA* 2012;**109**:2412–7.

Vidoudez C, Casotti R, Bastianini M *et al.* Quantification of dissolved and particulate polyunsaturated aldehydes in the Adriatic Sea. *Marine Drugs* 2011a;**9**:500–13.

Vidoudez C, Nejstgaard JC, Jakobsen HH *et al.* Dynamics of dissolved and particulate polyunsaturated aldehydes in mesocosms inoculated with different densities of the diatom *Skeletonema marinoi*. *Marine Drugs* 2011b;**9**:345–58.

Vidoudez C, Pohnert G. Growth phase specific release of polyunsaturated aldehydes by the diatom *Skeletonema marinoi*. *J Plankton Res* 2008;**30**:1305–13.

Volk RB. Screening of microalgal culture media for the presence of algicidal compounds and isolation and identification of two bioactive metabolites, excreted by the cyanobacteria *Nostoc insulare* and *Nodularia harveyana*. *J Appl Phycol* 2005;**17**:339–47.

Volk RB. Antialgal activity of several cyanobacterial exometabolites. *J Appl Phycol* 2006;**18**:145–51.

von Dassow P, Montresor M. Unveiling the mysteries of phytoplankton life cycles: patterns and opportunities behind complexity. *J Plankton Res* 2011;**33**:3–12.

Wagner-Döbler I, Biebl H. Environmental biology of the marine *Roseobacter* lineage. *Annu Rev Microbiol* 2006;**60**:255–80.

Wang H, Butt L, Rooks P *et al.* Characterisation of algicidal bacterial exometabolites against the lipid-accumulating diatom *Skeletonema* sp. *Algal Res* 2016a;**13**:1–6.

Wang H, Hill RT, Zheng TL *et al.* Effects of bacterial communities on biofuel-producing microalgae: stimulation, inhibition and harvesting. *Crit Rev Biotechnol* 2016b;**36**:341–52.

Wang H, Tomasch J, Jarek M *et al.* A dual-species co-cultivation system to study the interactions between *Roseobacters* and dinoflagellates. *Front Microbiol* 2014;**5**:311.

Wang H, Tomasch J, Michael V *et al.* Identification of genetic modules mediating the Jekyll and Hyde interaction of *Dinoroseobacter shibae* with the dinoflagellate *Prorocentrum minimum*. *Front Microbiol* 2015;**6**:1262.

Wang M-H, Peng P, Liu Y-M *et al.* Algicidal activity of a dibenzofuran-degrader *Rhodococcus* sp. *J Microbiol Biotechn* 2013;**23**:260–6.

Wang X, Gong L, Liang S *et al.* Algicidal activity of rhamnolipid biosurfactants produced by *Pseudomonas aeruginosa*. *Harmful Algae* 2005;**4**:433–43.

Wang X, Li ZJ, Su J *et al.* Lysis of a red-tide causing alga, *Alexandrium tamarense*, caused by bacteria from its phycosphere. *Biol Control* 2010;**52**:123–30.

Waters CM, Bassler BL. Quorum sensing: cell-to-cell communication in bacteria. *Annu Rev Cell Dev Biol* 2005;**21**:319–46.

Wear EK, Carlson CA, James AK *et al.* Synchronous shifts in dissolved organic carbon bioavailability and bacterial community responses over the course of an upwelling-driven phytoplankton bloom. *Limnol Oceanogr* 2015;**60**:657–77.

Weber RJM, Selander E, Sommer U *et al.* A stable-isotope mass spectrometry-based metabolic footprinting approach to analyze exudates from phytoplankton. *Mar Drugs* 2013;**11**:4158–75.

Wigglesworlth-Cooksey B, Cooksey KE, Long R. Antibiotic from the marine environment with antimicrobial fouling activity. *Environ Toxicol* 2007;**22**:275–80.

Wilhelm SW, Suttle CA. Viruses and nutrient cycles in the sea - viruses play critical roles in the structure and function of aquatic food webs. *F1000 Biol Rep* 2012;**4**:17.

Williams P, Winzer K, Chan WC *et al.* Look who's talking: communication and quorum sensing in the bacterial world. *Philos T Roy Soc B* 2007;**362**:1119–34.

Wu YH, Liu JT, Yang LZ *et al.* Allelopathic control of cyanobacterial blooms by periphyton biofilms. *Environ Microbiol* 2011;**13**:604–15.

Xie L, Altindal T, Chattopadhyay S *et al.* Bacterial flagellum as a propeller and as a rudder for efficient chemotaxis. *P Natl Acad Sci USA* 2011;**108**:2246–51.

Yamaguchi T, Kobayashi Y, Adachi K *et al.* Argimicins B and C, new anti-cyanobacterial compounds produced by *Sphingomonas* sp. M-17. *J Antibiot* 2003;**56**:655–7.

Yates EA, Philipp B, Buckley C *et al.* N-acylhomoserine lactones undergo lactonolysis in a pH-, temperature-, and acyl chain length-dependent manner during growth of *Yersinia pseudotuberculosis* and *Pseudomonas aeruginosa*. *Infect Immun* 2002;**70**:5635–46.

Yoshikawa K, Adachi K, Nishijima M *et al.* Beta-cyanoalanine production by marine bacteria on cyanide-free medium and its specific inhibitory activity toward cyanobacteria. *Appl Environ Microb* 2000;**66**:718–22.

Zhang H, Peng Y, Zhang S *et al.* Algicidal effects of prodigiosin on the harmful algae *Phaeocystis globosa*. *Front Microbiol* 2016;**7**:602.

Zheng X, Zhang B, Zhang J *et al.* A marine algicidal actinomycete and its active substance against the harmful algal bloom species *Phaeocystis globosa*. *Appl Microbiol Biot* 2013;**97**: 9207–15.

Zhou J, Chen G, Zhu X *et al.* A review of the relationship between algae and bacteria in harmful algal blooms. *Acta Ecol Sin/Shengtai Xuebao* 2015;**34**: DOI: 10.5846/stxb201303060361.

Ziesche L, Bruns H, Dogs M *et al.* Homoserine lactones, methyl oligohydroxybutyrates, and other extracellular metabolites of macroalgae-associated bacteria of the Roseobacter clade: identification and functions. *ChemBioChem* 2015;**16**:2094–107.