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MINI-REVIEW

Microorganisms living on macroalgae: diversity, interactions, and biotechnological applications

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Abstract Marine microorganisms play key roles in every marine ecological process, hence the growing interest in studying their populations and functions. Microbial communities on algae remain underexplored, however, despite their huge biodiversity and the fact that they differ markedly from those living freely in seawater. The study of this microbiota and of its relationships with algal hosts should provide crucial information for ecological investigations on algae and aquatic ecosystems. Furthermore, because these microorganisms interact with algae in multiple, complex ways, they constitute an interesting source of novel bioactive compounds with biotechnological potential, such as dehalogenases, antimicrobials, and alga-specific polysaccharidases (e.g., agarases, carrageenases, and alginate lyases). Here, to demonstrate the huge potential of alga-associated organisms and their metabolites in developing future biotechnological applications, we first describe the immense diversity and density of these microbial biofilms. We further describe their complex interactions with algae, leading to the production of specific bioactive compounds and hydrolytic enzymes of biotechnological interest. We end with a glance at their potential use in medical and industrial applications.

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Introduction: surface-associated marine microorganisms

Marine microorganisms live freely in seawater (planktonic microorganisms) or attached to biotic or abiotic surfaces. Microorganisms on a surface commonly form a biofilm, defined as "*an assemblage of microbial cells that is irreversibly associated with a surface and enclosed in a matrix of primarily polysaccharide material*" (Donlan 2002). This matrix, called the exopolysaccharide layer, allows close spatial proximity, enhancing communication and interactions among bacteria and between bacteria and their host (Kilian et al. 1985; Pasmore and Costerton 2003; Wilson et al. 2011). In the marine environment, where competition for space and nutrients is intense, the surfaces of marine eukaryotes such as invertebrates and algae offer a nutrient-rich habitat uniquely suited for microbial colonization and biofilm formation (Egan et al. 2008; Goecke et al. 2010). As such surfaces are highly complex and differentiated, marine microbial biofilms should constitute a huge source of diversity, and the bacterial communities forming them should differ considerably in composition from populations of pelagic bacteria. Oddly, although bacteria in marine environments are most often surface-associated, previous investigations have preponderantly focused on the diversity of planktonic microorganisms rather than on microbial epibionts. Yet although investigators are increasingly using both culture-dependent and culture-independent methods to zoom in on microbial symbionts living on the surfaces of organisms such as corals, sponges, tunicates, and macroalgae (Erwin et al. 2011; Rohwer et al. 2002; Taylor et al. 2003; Wegley et al. 2007; Wilson et al. 2010), the biotechnological potential of these symbionts remains little discussed. In this review we focus on microbial

biofilms on marine macroalgae, including their potential importance in developing future biotechnological applications. We discuss the diversity and density of these biofilms and the factors influencing the microbial communities that live on diverse algal species. We further outline interactions between algae and their epibionts leading to the production of metabolites of biotechnological interest. Particularly, we review the state of the art on algal-specific polysaccharidases from seaweed-associated bacteria. Finally, we draw attention to the potential importance of these microorganisms and their metabolites, such as secondary bioactive compounds and specific hydrolytic enzymes, for biotechnological applications in diverse industrial fields.

Diversity of microorganisms on algae

Microorganisms are very abundant on the surfaces of marine organisms ($>1.1\times10^8$ microorganisms/cm^2) (Cundell et al. 1977). Although the microorganisms observed and identified on the surfaces of diverse algae include yeasts, fungi, and protists (Armstrong et al. 2000; Cundell et al. 1977; Genilloud et al. 1994; Schaumann and Weide 1995; Uchida and Murata 2004), most available reports on alga-associated microbial populations concern bacteria. Therefore this review focuses mainly on alga-associated bacterial communities.

The density of bacteria on algal surfaces has been estimated by cell counts under the microscope (Cundell et al. 1977), by culture-based methods (Mazure and Field 1980), and by molecular approaches (Armstrong et al. 2000). Mean densities between 10^6 and 10^9 bacteria/cm^2 algal surface have been recorded. There is some controversy regarding the composition of bacterial communities on algae. Bacterioplankton studies have shown most marine bacteria to be gram negative, but recent studies on marine-sediment-associated bacteria have revealed a large proportion of gram-positive bacteria, too (Gontang et al. 2007). Table 1 shows the most abundantly represented phyla (and classes or orders) of bacteria identified on diverse algal species, with the sampling location and season. Gram-negative bacteria of the phyla *Bacteroidetes* and *Proteobacteria* emerge as the most abundant, having been found on practically all the listed algal species (Table 1). Although gram-negative bacteria appear to preponderate, gram-positive species are also present. In particular, gram-positive bacteria of the phyla *Actinobacteria* and *Firmicutes* have been observed on most algae (Table 1). On some species or in a particular season, other bacterial phyla can also be abundant. For instance, Bengtsson et al. found peptidoglycan-less *Planctomycetes* species to dominate the bacterial biofilm on the kelp *Laminaria hyperborea* for long periods of the year (Bengtsson et al. 2010, 2013; Bengtsson and Øvreås 2010). Ocean surface water shows a phylum distribution quite similar to that of algal surface bacteria, the most abundantly represented phylum being the *Proteobacteria* (particularly the class *Alpha-proteobacteria*) (Morris et al. 2002), followed by the *Bacteroidetes*, *Actinobacteria*, *Planctomycetes*, and *Chloroflexi* (Longford et al. 2007). At the bacterial genus and species levels, however, recent investigations have revealed notable differences in composition between epibacterial communities and the surrounding bacterioplankton communities (Burke et al. 2011b; Lachnit et al. 2011; Longford et al. 2007). This suggests that colonization patterns are host-specific and strongly influenced by the seaweed, because of physico-chemical constraints, such as cell wall component diversity (Michel et al. 2010a; Popper et al. 2011), and/or active defense mechanisms (Cosse et al. 2007; Potin et al. 2002). Table 1 further shows that the sampling season and region and the algal species or phylum can influence community composition. In fact, diverse factors shape the composition of alga-associated bacterial populations:

(i) Recent studies on bacterial biofilm composition have shown it to vary considerably with the algal phylum (green, brown, or red algae) and, to a lesser extent, with the algal species (Lachnit et al. 2009; Longford et al. 2007). Longford et al. compared the bacterial beta-(between host) and alpha-(within host) diversity of the marine sponge *Cymbastela concentrica* and two co-habiting algae species, the red alga *Delisea pulchra* and the green alga *Ulva australis* (Longford et al. 2007). Between the two algal species, the community patterns were very similar at bacterial phylum level, but at bacterial species level little overlap was observed. Lachnit et al. focused on compositional variability among the bacterial communities associated with diverse species of the three algal phyla *Rhodophyta*, *Chlorophyta*, and *Phaeophyta* (Lachnit et al. 2009). They found that host phylum seems to contribute more than host species to dissimilarity in epibacterial composition, explaining this dissimilarity on the basis of different physico-chemical properties and metabolite compositions and more or less effective defense mechanisms (Potin et al. 2002) and/or attractants (Pasmore and Costerton 2003). For instance, brown algae produce and secrete large amounts of mannitol (Gravot et al. 2010), a main carbon storage compound (Michel et al. 2010b). This organic exudate was recently shown to affect the formation of biofilms of marine bacteria such as *Pseudolatermonas* spp. 3J6 and D41 and *Zobellia galactanivorans* (Salaün et al. 2012). This latter microorganism, which was isolated from the red alga *Delesseria sanguinea* (Barbeyron et al. 2001), is a model bacterium for the study of bacteria–seaweed interactions and particularly the bioconversion of algal polysaccharides (Michel and Czjzek 2013).

Table 1 Most represented bacterial phyla (class and order) on diverse algal species

Algae phyla	Algae specie	Sample region	Sample season	Most bacterial represented phylum (and/or class)	Source
Phaeophyta	*Fucus vesiculosus*	Kiel fjord (Western Baltic Sea, Germany)	Winter	*Bacteroidetes*, *Planctomycetes*, *Proteobacteria* (*Alpha* and *Gamma*)	(Lachnit et al. 2011)
			Summer	*Bacteroidetes*, *Cyanobacteria*, *Proteobacteria* (*Alpha* (*Rhodobacterales*)), *Verrucomicrobia*	
	Fucus vesiculosus	Kiel fjord (Western Baltic Sea, Germany)	Winter	*Actinobacteria*, *Bacteroidetes* (*Flavobacteria*), *Firmicutes* (*Bacilli*)	(Goecke et al. 2013)
			Summer	*Bacteroidetes* (*Flavobacteria*), *Firmicutes* (*Bacilli*), *Proteobacteria* (*Gamma*)	
	Dictyota bartayresiana	Island of Curacao (Netherlands Antilles)	(Not specified)	*Bacteroidetes*, *Cyanobacteria*, *Proteobacteria*	(Barott et al. 2011)
	Laminaria digitata	Roscoff (France)	(Not specified)	*Actinobacteria*, *Bacteroidetes*, *Proteobacteria* (*Alpha* and *Gamma*)	(Salaün et al. 2010)
	Laminaria saccharina	Kiel fjord (Western Baltic Sea, Germany)	Winter and Summer	*Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria* (*Alpha*, *Beta* and *Gamma*)	(Wiese et al. 2009)
	Laminaria hyperborea	Southwest coast of Norway	Summer	*Plantomycetes*, *Proteobacteria* (*Alpha*, *Beta* and *Gamma*), *Verrucomicrobia*	(Bengtsson et al. 2010; Bengtsson and Øvreås 2010)
			Winter	*Bacteroidetes*, *Cyanobacteria*, *Plantomycetes*, *Proteobacteria* (*Alpha*, *Beta* and *Gamma*), *Verrucomicrobia*	
Rodophyta	*Gracileria vermiculophylla*	Kiel fjord (Western Baltic Sea, Germany)	Winter	*Bacteroidetes*, *Proteobacteria* (*Alpha* (*Rhodobacterales* and *Rhizobiales*))	(Lachnit et al. 2011)
			Summer	*Bacteroidetes*, *Proteobacteria* (*Alpha* (*Rhodobacterales*))	
	Jania rubens	Cap Zebib (northern coast of Tunisia)	Summer	*Bacteroidetes*, *Proteobacteria* (*Alpha* and *Gamma*)	(Ismail-Ben Ali et al. 2011)
	Delisea pulchra	Bare Island (Sydney, Australia)	Summer	*Bacteroidetes*, *Proteobacteria* (*Alpha*), *Planctomycetes*	(Fernandes et al. 2012)
	Delesseria sanguinea	Kiel fjord (Western Baltic Sea, Germany)	Winter	*Actinobacteria*, *Bacteroidetes* (*Flavobacteria*), *Firmicutes* (*Bacilli*), *Proteobacteria* (*Gamma*)	(Goecke et al. 2013)
			Summer	*Bacteroidetes* (*Flavobacteria*), *Firmicutes* (*Bacilli*), *Proteobacteria* (*Gamma*)	
Chlorophyta	*Ulva intestinalis*	Kiel fjord (Western Baltic Sea, Germany)	Winter	*Bacteroidetes*, *Proteobacteria* (*Alpha* (*Rhizobiales*) and *Gamma*)	(Lachnit et al. 2011)
			Summer	*Bacteroidetes*, *Proteobacteria* (*Alpha* (*Rhodobacterales* and *Rhizobiales*) and *Gamma*)	
	Ulva sp.	Wembury Beach, Devon, UK	(Not specified)	*Bacteroidetes* (*Flavobacteria*), *Proteobacteria* (*Alpha* (*Rhodobacterales*))	(Tait et al. 2009)
	Ulva australis	Bare Island (Sydney, Australia)	Winter	*Bacteroidetes*, *Planctomycetes*, *Proteobacteria* (*Alpha* and *Gamma*)	(Burke et al. 2011b; Tujula et al. 2010)
	Bryopsis hypnoides	Pacific Mexican coast	Winter	*Bacteroidetes* (*Flavobacteria* and *unclassified*), *Mollicutes* (*Mycoplasmataceae*),	(Hollants et al. 2011)
	Bryopsis pennata			*Bacteroidetes* (*Flavobacteria*)	
	Caulerpa taxifolia	Mediterranean	(Not specified)	*Cytophaga-Flexibacter-Bacteroides* (*CFB*), *Proteobacteria* (*Alpha* and *Beta*)	(Meusnier et al. 2001)
		Tahiti		*Proteobacteria* (*Alpha* and *Delta*)	
		Philippines		*Proteobacteria* (*Alpha*, *Delta* and *Gamma*)	
		Australia		*Cytophaga-Flexibacter-Bacteroides* (*CFB*), *Proteobacteria* (*Alpha* and *Beta*)	

(ii) The part of the thallus sampled and its age also influence both the composition and the specificity of the bacterial population. On the brown alga *Laminaria saccharina*, for example, Staufenberger et al. (2008) found a greater bacterial diversity on the old phyloid than on any other part of the alga, explaining it on the basis of tissue age/mechanical stress: this tissue should contain more damaged cells vulnerable to bacterial decomposition, enhancing bacterial colonization. Furthermore, the association appeared most specific (i.e., between-specimen variability was lowest) on the meristem (where new tissue is formed) and cauloid. On all parts of the alga, however, the bacterial communities differed markedly from those of the surrounding seawater. The authors also point out that the composition of the bacterial community present on the substratum-anchored rhizoid is likely to reflect the presence, in the substratum, of other marine organisms with their own surface communities.

(iii) Seasonal changes in the composition of alga-associated bacterial populations have also been recorded. Mazure and Field (1980) observed on the brown alga *Laminaria saccharina* a predominance of mesophilic bacteria in summer, with a switch to a more psychrophilic population in winter. A similar seasonal shift was observed on *Laminaria digitata* (Corre and Prieur 1990; Salaün 2009). Furthermore, bacterial abundance can be two to three times greater in summer, likely because the higher temperature favors enhanced microbial metabolism (Rao 2010). Moreover, Stratil et al. (2013) studied the shift in diversity and density of bacterial populations on *Fucus vesiculosus* cultured at different temperatures. They found 20 % of the bacterial diversity variation between host groups to be due to temperature, but bacterial density was not affected by this factor.

(iv) Rapid changes in bacterial community composition and abundance have also been observed between healthy and bleached (diseased) algal tissues. On diseased macroalgae, the density of bacteria and other microfoulers can be as much as 400 times that found on healthy tissues (Weinberger et al. 1994). Furthermore, comparative metagenomics applied to healthy and bleached tissues of *D. pulchra* has evidenced differences in bacterial taxa and functional genes (Fernandes et al. 2012). These shifts have been explained by reduced defenses in stressed thalli (due to high summer temperature), leading to colonization by opportunistic and pathogenic bacteria.

(v) Finally, Burke et al. (2011a), studying *Ulva australis*, observed intraspecies differences in bacterial community composition. They noted similar functional profiles for the communities found on different specimens, suggesting that (functional) genes, rather than bacterial species, may explain the diversity of bacterial epibionts on algae. These intraspecies differences were also observed on *F. vesiculosus* (Stratil et al. 2013). As only 20 % of the community variation could be explained by temperature changes, a large proportion of variation between hosts is left unexplained. This strengthens the 'functional profile' theory of Burke et al.

Alga-associated microorganisms produce specific enzymes and bioactive compounds

Microorganisms on algae, through their complex and numerous interactions with the host, constitute an immense source of bioactive compounds and specific polysaccharidases. Therefore, before discussing the biotechnological potential of algal epibionts and their metabolites, we will have a glance at microorganism–alga interactions and at the biotechnologically useful bioactive compounds and enzymes produced by alga-associated microorganisms.

Seaweed-associated bacteria produce alga-specific polysaccharidases

It is generally assumed that microorganisms benefit from the ready availability of a range of organic carbon sources produced by the host alga. Green, red, and brown algae produce a wide diversity of complex polysaccharides which are essential components of their cell walls (Popper et al. 2011). These polysaccharides constitute a crucial biomass in coastal ecosystems. Interestingly, in contrast to the polysaccharides of terrestrial plants, most algal polysaccharides are non-lignocellulosic and sulfated (Popper et al. 2011). Whereas lignocellulosic biomass consists of cellulose, lignin, and hemicelluloses, macroalgal biomass is much more complex. About ten different polysaccharides (e.g., agars, carrageenans, and ulvans) and as many monosaccharides (e.g., glucose, mannose, and xylose), are found over the three algal phyla (Jung et al. 2013). Accordingly, alongside common polysaccharidases (e.g., cellulases, beta-glucosidases, and amylases), very specific carbohydrate-active enzymes are found in microorganisms living on algae. Here we present the current state of knowledge on these enzymes (see http://www.cazy.org/, Cantarel et al. 2009), focusing solely on those characterized at both the molecular and biochemical levels, and particularly on those whose 3D structure has been determined (Table 2).

Carrageenases

Carrageenans and agars are sulfated galactans. They are the main cell wall components of red macroalgae (Popper et al 2011). Carrageeenases are currently divided into three classes according to the number of sulfate substituents per disaccharide

repeating unit which are specifically recognized: kappa- (one sulfate, EC 3.2.1.83), iota- (two sulfates, EC 3.2.1.157), and lambda-carrageenases (three sulfates, EC 3.2.1.-). All these enzymes cleave β-1,4 glycosidic bonds in carrageenans.

Kappa-carrageenase genes have been cloned from several *Pseudoalteromonas* species (Barbeyron et al. 1994; Kobayashi et al. 2012; Liu et al. 2011), from *Zobellia* species (Barbeyron et al. 1998; Liu et al. 2013), and from *Cellulophaga lytica* strain N5-2 (Yao et al. 2013). The corresponding enzymes belong to glycoside hydrolase family 16 (GH16) (Barbeyron et al. 1994). The kappa-carrageenase of *Pseudoalteromonas carrageenovora* adopts a β jelly-roll fold and displays a tunnel active site (Fig. 1a). These features suggest that this enzyme has an endo-processive mode of action (Michel et al. 2001a), and this prediction has been biochemically confirmed (Lemoine et al. 2009).

The first cloned iota-carrageenase genes originated from the marine bacterium *Alteromonas fortis* and from *Z. galactanivorans*, and their products defined the GH82 family (Barbeyron et al. 2000). Additional iota-carrageenase genes have been cloned from *Cellulophaga* sp. QY3, a flavobacterium isolated from the red alga *Grateloupia livida* (Ma et al. 2013), and from *Microbulbifer thermotolerans* JAMB-A94T, a deep-sea bacterium (Hatada et al. 2011). The iota-carrageenase CgiA of *A. fortis* adopts a right-handed β-helix fold with two additional domains (A and B) in the C-terminal region (Michel et al. 2001b). Upon substrate binding, the (α/β)-fold domain A shifts towards the β-helix cleft, forming a tunnel that encloses the iota-carrageenan chain (Fig. 1b), thus explaining the highly processive character of CgiA (Michel et al. 2003). A mechanistic study has demonstrated that CgiA is chloride ion dependent and that its catalytic residues are Glu245 and Asp247 (Rebuffet et al. 2010).

Lambda-carrageenases constitute a new GH family, unrelated to kappa- and iota-carrageenases (Guibet et al. 2007). Only two genes have been cloned so far, one from the seaweed-associated bacterium *P. carrageenovora* (Guibet et al. 2007) and one from the deep-sea bacterium *Pseudoalteromonas* sp. strain CL19 (Ohta and Hatada 2006). The products of these genes are highly similar (98 % sequence identity), explaining why no CAZY family number has yet been attributed (Cantarel et al. 2009). These large enzymes (~105 kDa) feature a low-complexity linker connecting two independent modules, an N-terminal domain predicted to fold as a β-propeller and a C-terminal domain of unknown function (Guibet et al. 2007).

Agarases

Agarases are divided into two classes, alpha-agarases (EC 3.2.1.158) and beta-agarases (EC 3.2.1.81), which respectively hydrolyze α-1,3 and β-1,4 linkages between neutral agarose motifs in agar chains. The first alpha-agarase activity was purified and characterized from *Alteromonas agarlyticus* 20 years ago (Potin et al. 1993). The gene was later cloned, revealing a large enzyme (154 kDa) with a complex modular architecture including five calcium-binding thrombospondin type 3 repeats, three family-6 carbohydrate-binding modules (CBM6s), and a C-terminal catalytic module defining a novel GH family (GH96) (Flament et al. 2007). Bioinformatic studies suggest that the CBM6s specifically bind agars and were acquired from modular GH16 beta-agarases (Michel et al. 2009). A highly similar alpha-agarase (72 % sequence identity) has also been cloned from *Thalassomonas* sp. JAMB-A33, a strain isolated from marine sediment (Hatada et al. 2006).

Beta-agarases are found in four unrelated CAZY families: GH16, GH50, GH86, and GH118 (Cantarel et al. 2009). The first beta-agarases to be both structurally and biochemically characterized were the GH16 beta-agarases *Zg*AgaA and *Zg*AgaB of *Z. galactanivorans* (Allouch et al. 2003; Jam et al. 2005). *Zg*AgaA is an extracellular monomeric enzyme with a GH16 module appended to a putative CBM and a PorSS secretion domain, while *Zg*AgaB is a dimeric lipoprotein anchored to the outer membrane (Jam et al. 2005). In both enzymes, the GH16 module displays a β jelly-roll fold with an open catalytic groove (Allouch et al. 2003). Two agar-binding sites have been identified in the structure of $Zg\text{AgaA}_{\text{GH16}}$ complexed with oligo-agars: one in the active site cleft and one at the external surface of the protein, explaining the high agar-fiber-degrading efficiency of this enzyme (Allouch et al. 2004). The crystal structure of a third beta-agarase from *Z. galactanivorans* has been solved recently. ZgAgaD has a longer catalytic groove with eight subsites (Fig. 1c) and is specific for unsubstituted agarose motifs (Hehemann et al. 2012a). Numerous GH16 beta-agarases have been cloned from bacteria isolated from seawater or marine sediments, but relatively few from seaweed-associated bacteria (Kim and Hong 2012; Oh et al. 2010; Schroeder 2003; Yang et al. 2011).

The first GH50 beta-agarase was cloned from *Vibrio* sp. JTO107, isolated from seawater in Japan (Sugano et al. 1993). So far, however, no GH50 gene has been cloned from an alga-associated microorganism. The first structure of a GH50 beta-agarase was determined last year: Aga50D from *Saccharophagus degradans* (Pluvinage et al. 2013). This bacterium was isolated from a halotolerant land plant in a salt marsh, and is thus not a genuine marine microorganism (Andrykovitch and Marx 1988). Aga50D features two domains, a $(\beta/\alpha)_8$-barrel connected to a small β-sandwich domain reminiscent of a CBM (Fig. 1d). The putative catalytic residues (Glu534 and Glu695) are located in an active site with a tunnel topology, in keeping with the exo-lytic mode of action of this beta-agarase (Pluvinage et al. 2013).

One of the first characterized beta-agarases (AgrA) was purified from *Pseudoalteromonas atlantica* Tc6, a

Table 2 Census of the algal-specific polysaccharidases from seaweed-associated bacteria

Protein	CAZY	Bacterial species	Associated algal species (or isolation habitat) B=brown alga, G=green alga, R=Red alga	Genbank	PDB	References
Carrageenases						
κ-carrageenase *Pc*CgkA	GH16	*Pseudoaltermonas carrageenovora* ATCC 43555	Seawater	CAA50624.1	1DYP	(Barbeyron et al. 1994; Michel et al. 2001a)
κ-carrageenase	GH16	*Pseudoalteromonas porphyrae* LL1	Decayed seaweed	ADD92366.1	–	(Liu et al. 2011)
κ-carrageenase *Zg*CgkA	GH16	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	CAZ94309.1	–	(Barbeyron et al. 1998)
κ-carrageenase	GH16	*Zobellia* sp. ZM-2	Decayed seaweed	AGS43006.1	–	(Liu et al. 2013)
ι-carrageenase *Af*CgiA	GH82	"*Alteromonas fortis*" ATCC 43554	Seawater	CAC07801.1	1H80 1KTW 3LMW	(Barbeyron et al. 2000; Michel et al. 2001b, 2003; Rebuffet et al. 2010)
ι-carrageenase *Zg*CgiA1	GH82	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	CAC07822.1	–	(Barbeyron et al. 2000)
ι-carrageenase *Zg*CgiA2	GH82	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	CAZ96312.1	–	(Rebuffet et al. 2010)
ι-carrageenase *Zg*CgiA3	GH82	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	CBW46642.1	–	(Rebuffet et al. 2010)
ι-carrageenase CgiA	GH82	*Cellulophaga* sp. QY3	*Grateloupia livida* (R)	AEV89930.1	–	(Ma et al. 2013)
ι-carrageenase CgiB	GH82	*Cellulophaga* sp. QY3	*Grateloupia livida* (R)	AGN70890.1	–	(Ma et al. 2013)
λ-carrageenase *Pc*CglA	GHnc	*Pseudoaltermonas carrageenovora* ATCC 43555	Seawater	CAL37005.1	–	(Guibet et al. 2007)
λ-carrageenase CglA	GHnc	*Pseudoalteromonas* sp. CL19	Deep-sea sediment	BAF35571.1	–	(Ohta and Hatada 2006)
Agarases						
α-agarase *Aa*AgaA	GH96	"*Alteromonas agarlytica*" DSM 12513	Seawater	AAF26838.1	–	(Potin et al. 1993; Flament et al. 2007)
α-agarase Aga33	GH96	*Thalassomonas agarivorans* JAMB A33	Deep-sea sediment	BAF44076.1	–	(Hatada et al. 2006)
β-agarase *Zg*AgaA	GH16	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	CAZ98338.1	1O4Y 1URX	(Allouch et al. 2003, 2004; Jam et al. 2005)
β-agarase *Zg*AgaB	GH16	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	AAF21821.1	1O4Z 4ATF	(Allouch et al. 2003; Jam et al. 2005; Hehemann et al. 2012a)
β-agarase *Zg*AgaD	GH16	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	CAZ98378.1	4ASM	(Hehemann et al. 2012a)
β-agarase AagA	GH16	*Pseudoalteromonas gracilis* B9	*Gracilaria gracilis* (R)	AAF03246.1	–	(Schroeder 2003)
β-agarase	GH16	*Pseudoalteromonas* sp. AG4	*Chondrus crispus* (R)	ADD60418.1	–	(Oh et al. 2010)
β-agarase AgaYT	GH16	*Flammeovirga yaeyamensis* YT	*Gracilaria tenuistipitata* (R)	AEK80424.1	–	(Yang et al. 2011)
β-agarase AgaG1	GH16	*Alteromonas* sp. GNUM-1	*Sargassum serratifolium* (B)	AGW43026.1	–	(Kim et al. 2012)
exo-β-agarase AgaD	GH50	*Saccharophagus degradans* 2-40	*Spartina alterniflora* (salt marsh plant)	ABD81904.1	4BQ2 4BQ3 4BQ4 4BQ5	(Pluvinage et al. 2013)
β-agarase II (AgrA)	GH86	*Pseudoalteromonas atlantica* T6c	*Palmaria palmata* (R)	ABG40858.1	–	(Belas 1989)
β-agarase AgaC	GH118	*Vibrio* sp. PO-303	Seawater	BAF03590.1	–	(Dong et al. 2006)
β-agarase AgaB	GH118	*Pseudoalteromonas* sp. CY24	Seawater	AAQ56237.1	–	(Ma et al. 2007)
Porphyranases						
β-porphyranase *Zg*PorA	GH16	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	CBM41182.1	3ILF 4ATE	(Hehemann et al. 2010)
β-porphyranase *Zg*PorB	GH16	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	CAZ95074.1	3JUU	(Hehemann et al. 2010)
β-porphyranase *Bp*GH16B	GH16	*Bacteroides plebeius* DSM 17135	Japanese gut microbiota	EDY95423.1	4AWD	(Hehemann et al. 2012b)

Table 2 (continued)

Protein	CAZY	Bacterial species	Associated algal species (or isolation habitat) B=brown alga, G=green alga, R=Red alga	Genbank	PDB	References
β-porphyranase *Bp*GH86A	GH86	*Bacteroides plebeius* DSM 17135	Japanese gut microbiota	EDY95427.1	4AW7	(Hehemann et al. 2012b)
α-1,3-(3,6-anhydro)-L-galactosidases						
ZgAhgA	GH117	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	CBM41465.1	3P2N	(Rebuffet et al. 2011)
*Sd*NABH	GH117	*Saccharophagus degradans* 2-40	*Spartina alterniflora* (salt marsh plant)	ABD81917.1	3R4Y 3R4Z	(Ha et al. 2011)
*Bp*GH117	GH117	*Bacteroides plebeius* DSM 17135	Japanese gut microbiota	EDY95405.1	4AK5 4AK6 4AK7	(Hehemann et al. 2012b)
Laminarinases						
Algal laminarin-specific β-glucanase *Zg*LamA	GH16	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	CAZ96583.1	4BOW 4BPZ 4BQ1	(Labourel et al. 2014)
Fucoidanases						
Fucoidanase *Mf*FcnA	GH107	*Marineflexile fucanivorans* SW5	Alginate-extraction factory	CAI47003.1	–	(Colin et al. 2006)
Alginate lyases						
Alginate lyase *Zg*AlyA4	PL6	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	CAZ98265.1	–	(Thomas et al. 2012)
Endo-guluronate lyase *Zg*AlyA1	PL7	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	CAZ95239.1	3ZPY	(Thomas et al. 2012) (Thomas et al. 2013)
Exo-alginate lyase *Zg*AlyA5	PL7	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	CAZ98266.1	4BE3	(Thomas et al. 2012) (Thomas et al. 2013)
Poly-mannuronate lyase AlxM	PL7	*Photobacterium* sp. ATCC 43367	*Sargassum fluitans* (B)	CAA49630.1	–	(Malissard et al. 1993)
Alginate lyase Aly1	PL7	*Streptomyces* sp. ALG-5	green seaweed (G)	AAP47162.1	–	(Kim et al 2009)
Alginate lyase AlyVI	PL7	*Vibrio* sp. QY101	*Laminaria* sp. (B)	AAP45155.1	–	(Han et al. 2004)
Alginate lyase *Zg*AlyA7	PL14	*Zobellia galactanivorans* Dsij	*Delesseria sanguinea* (R)	CAZ98462.1	–	(Thomas et al. 2012)
Poly-MG alginate lyase alyPEEC	PL18	*Pseudoalteromonas elyakovii* IAM14594	*Laminaria* sp. (B)	AAD16034.1	–	(Sawabe et al. 2001)
Alginate lyase Aly-SJ02	PL18	*Pseudoalteromonas* sp. SM0524	Kelp (B)	ACB87607.1	–	(Li et al. 2011)
Ulvan lyases						
Ulvan lyase	PLnc	*Persicivirga ulvanivorans* PLR	Feces of *Aplysia punctata* (sea hare) feed with *Ulva* sp. (G)	AEN28574.1	–	(Nyvall Collén et al. 2011)

Only enzymes characterized at the molecular and biochemical level have been considered. Some bacterial sequences from other environments have been added when they constitute representative enzymatic activities or 3D structure

gammaproteobacterium isolated in Canada from the red alga *Rhodymedia palmata* (Yaphe 1957). Its gene remained an orphan sequence for a long time (Belas 1989), before defining the GH86 family (Cantarel et al. 2009). No other GH86 beta-agarase has been characterized from alga-associated bacteria.

The GH118 family includes only eight sequences from marine bacteria, and none of them was isolated from a seaweed-associated bacterium. The first GH118 beta-agarase was cloned from *Vibrio* sp. PO-303 (Dong et al. 2006). The beta-agarase of *Pseudoalteromonas* sp. CY24 has also been extensively characterized, revealing a large binding site with 12 subsites. This GH118 enzyme proceeds according to a mechanism of inversion of the anomeric configuration (Ma et al. 2007), in contrast to GH16 beta-agarases, which act via a retaining mechanism (Jam et al. 2005). The families GH50 and GH86 are also predicted to encompass retaining enzymes (Pluvinage et al. 2013). Currently, there is no GH86 or GH118 beta-agarase of known 3D structure, although a note mentions the crystallization of a beta-agarase from *Pseudoalteromonas* sp. CY24 (Ren et al. 2010).

Porphyranases

Porphyran is the usual name of the agar extracted from red algae of the genus *Porphyra*. The porphyran backbone is composed of ~30 % agarose repetition moieties (LA-G), the remaining moieties being essentially L-galactopyranose-6-sulfate (L6S) linked via an α-1,3 bond to a beta-D-galactopyranose (G) residue. A porphyran repetition moiety (L6S-G) is linked via a β-1,4 linkage to either another porphyran moiety or to an agarose moiety (Correc et al. 2011). Such a hybrid structure is usual for agars, and the number of porphyran motifs varies according to the red algal species (Popper et al. 2011). Recently, a new class of enzymes has been discovered in the genome of *Z. galactanivorans*: β-porphyranases, which specifically hydrolyze the β-1,4 linkage between porphyran motifs in agars. These enzymes define a new subfamily within the GH16 family. The crystal structures of *Zg*PorA (Fig. 1e) and *Zg*PorB reveal a porphyran binding mode involving conserved basic amino acids (Hehemann et al 2010). The fine differences in substrate specificity between the β-agarases and β-porphyranases of *Z. galactanivorans* have been further studied, and a comprehensive model for this complex agarolytic system has been proposed (Hehemann et al. 2012a). Fascinatingly, β-porphyranase genes from algal epibionts have been found in human gut bacteria isolated from Japanese individuals, suggesting that edible seaweeds with their associated marine bacteria were the route through which the gut bacteria acquired these novel polysaccharidases (Hehemann et al. 2010). This hypothesis is strengthened by the experimental demonstration that the Japanese gut bacterium *Bacteroides plebeius* can grow on porphyran (Hehemann et al. 2012b). Moreover, the putative glycoside hydrolases BpGH16B and BpGH86A have been characterized as active β-porphyranases. The structure of BpGH86A in a complex with an oligo-porphyran has also been solved (Fig. 1f), revealing a TIM barrel domain with an extended substrate-binding cleft and two accessory β-sandwich domains (Hehemann et al. 2012b). Thus, GH86 enzymes constitute a polyspecific family including both β-agarases and β-porphyranases.

α-1,3-(3,6-Anhydro)-L-galactosidases

Z. galactanivorans has also been pivotal in the discovery of a third class of enzymes involved in the catabolism of agars: the hypothetical protein Zg4663, distantly related to GH43 enzymes, has emerged as a specific α-1,3-galactosidase catalyzing the removal of 3,6-anhydro-L-galactose residues from the non-reducing ends of oligo-agars released by β-agarases, hence the name α-1,3-(3,6-anhydro)-L-galactosidase (*Zg*AhgA, also known as α-1,3-L-neoagarooligosaccharide hydrolase). It defines a new family of glycoside hydrolases, the GH117 family (Rebuffet et al. 2011). AhgA features a helix-turn-helix (HTH) domain connected to a five-bladed β-propeller domain and forms a dimer by swapping of the HTH domain (Fig. 1g). The putative catalytic residues, partially conserved with GH43 enzymes, are located at the bottom of the funnel-like active site. The mechanism of *Zg*AhgA is cation dependent, and a zinc ion has been identified in the active site, with an unusual coordination sphere occupied by water molecules. The amino acids binding these water molecules (and thus indirectly this cation) are strictly conserved with the GH117 family (Rebuffet et al. 2011). Two homologs of *Zg*AhgA have been characterized more recently, *Sd*NABH from *S. degradans* and *Bp*GH117 from *B. plebeius*. While no cation was found in the structure of *Sd*NABH (Ha et al. 2011), *Bp*GH117 features a magnesium ion at the position conserved with *Zg*AhgA (Hehemann et al. 2012c), suggesting a degree of plasticity for this cation-binding site. The structure of an inactive mutant of *Bp*GH117 has also been determined, in a complex with neoagarobiose, identifying key residues for substrate recognition and catalysis. A mutagenesis approach has confirmed the involvement of five residues in catalysis: Asp90, Asp245, and Glu303 (conserved in family GH43), Glu167 (involved in the cation-binding site), and His302 (Hehemann et al. 2012c).

Alginate lyases

Alginate is a polymer of D-mannuronate and of its C5-epimer L-guluronate. It is an expolysaccharide in some bacteria and also the main cell wall compound of brown algae (Popper et al. 2011). Interestingly, genomic analysis has provided evidence that the common ancestor of brown algae acquired

the alginate biosynthesis pathway from actinobacteria (Michel et al. 2010a). This highlights the importance of associated bacteria in the evolution of macroalgae. Alginate lyases (EC 4.2.2.3) are the key enzymes in alginate degradation and remodeling, to be found in seven polysaccharide lyase families: PL5, PL6, PL7, PL14, PL15, PL17, and PL18. Despite the importance of algal alginate as renewable biomass, most of the characterized alginate lyases originate from alginate-producing bacteria and from terrestrial bacteria feeding on bacterial alginate (Cantarel et al. 2009). Only five genes have been cloned from seaweed-associated bacteria: three PL7 genes (Han et al. 2004; Kim et al. 2009; Malissard et al. 1993) and two PL18 genes (Li et al. 2011; Sawabe et al. 2001). Knowledge in this field has recently advanced with the characterization of the alginolytic system of *Z. galactanivorans* (Thomas et al. 2012). This flavobacterium possesses seven alginate lyase genes (two PL6, three PL7, one PL14, and one PL17 gene) and a PL15 gene of uncertain specificity. Five of these genes are organized in clusters: a small cluster (*alyA4*, *alyA5*, and *alyA6*) and a large cluster including *alyA2*, *alyA3*, and numerous carbohydrate-related genes predicted to be involved in alginate uptake and assimilation and in transcriptional regulation. These clusters have been shown to be genuine operons induced by alginate. *Zg*AlyA1, *Zg*AlyA4, *Zg*AlyA5, and *Zg*AlyA7 have been overexpressed in *Escherichia coli* and confirmed to be active alginate lyases. *Zg*2622 and *Zg*2614 are, respectively, a dehydrogenase and a kinase, further converting the terminal unsaturated monosaccharides released by alginate lyases to 2-keto-3-deoxy-6-phosphogluconate (Thomas et al. 2012). An in-depth study has demonstrated that *Zg*AlyA1 (PL7) is an endolytic guluronate lyase (EC 4.2.2.11), and *Zg*AlyA5 (PL7) cleaves unsaturated units, α-L-guluronate, or β-D-manuronate residues at the nonreducing ends of oligo-alginates in an exolytic fashion (EC 4.2.2.-). Despite a common jelly-roll fold, these striking differences in mode of action are due to different active site topologies: an open cleft in *Zg*AlyA1 (Fig. 1h), whereas *Zg*AlyA5 displays a pocket topology due to the presence of additional loops partially obstructing the catalytic groove (Fig. 1i). Lastly, in contrast to PL7 alginate lyases from terrestrial bacteria, both enzymes proceed according to a calcium-dependent mechanism, suggesting an exquisite adaptation to their natural substrate in the context of brown algal cell walls (Thomas et al. 2013).

Fucoidanases

Fucoidans are sulfated polysaccharides containing α-L-fucose residues and present in the cell wall of brown algae. They encompass a continuous spectrum of highly ramified polysaccharides, ranging from high-uronic-acid, low-sulfate polymers with significant proportions of D-xylose, D-galactose, and D-mannose to highly sulfated homofucan molecules (Popper et al 2011). Only one fucanolytic gene has been cloned to date: the fucoidanase *fncA* from *Mariniflexile fucanivorans* SW5 (Colin et al. 2006). This marine flavobacterium was isolated from a water-treatment facility that recycles the effluent from an algal alginate extraction plant (Barbeyron et al. 2008; Descamps et al. 2006). FcnA encompasses an N-terminal catalytic module (~400 residues), three immunoglobulin-like modules, and a PorSS secretion module. A recombinant protein including the N-terminal module and the immunoglobulin-like modules has been overexpressed in *E. coli*, purified, and shown to retain the same activity as the wild-type enzyme. This fucoidanase releases as end products a tetrasaccharide and a hexasaccharide, and cleaves the α-1,4 glycosidic bonds between L-fucose-2,3-disulfate-α-1,3-L-fucose-2-sulfate repeating units. The N-terminal catalytic module displays ~25 % identity to two patented fucoidanases from the bacterial strain SN-1009, and together these three proteins define a novel family of glycoside hydrolases, family GH107 (Colin et al. 2006).

Laminarinases

Laminarin, the storage polysaccharide of brown algae, is a small vacuolar beta-1,3-glucan containing ~25 glucosyl residues and some occasional β-1,6-linked branches. It includes two series, the minor G-series, containing only glucose residues, and the more abundant M-series, displaying a D-mannitol residue at the reducing end (Read et al. 1996). The unique presence of mannitol in laminarin is also explained by the horizontal gene transfer event involving the common ancestor of brown algae and an ancestral actinobacterium (Michel et al. 2010b). Laminarinases (EC 3.2.1.6 and 3.2.1.39) are found in several GH families (GH16, GH17, GH55, GH64, GH81, and GH128). Numerous beta-1,3-glucanases of terrestrial bacteria have been characterized in the context of the degradation of cell-wall beta-1,3-glucans of fungi, oomycetes, and land plants. Amazingly, however, among all the characterized beta-1,3-glucanases reported in the CAZY database (Cantarel et al. 2009), only one laminarinase gene has been cloned from a seaweed-associated bacterium: the GH16 laminarinase *Zg*LamA of *Z. galactanivorans* (Labourel et al. 2014). The 3D structure of *Zg*LamA$_{GH16}$ and of two enzyme–substrate complexes, one with laminaritetraose and one with a trisaccharide of 1,3-1,4-β-D-glucan, have been determined this year. Compared to other GH16 laminarinases, ZgLamA$_{GH16}$ contains a unique additional loop which gives a bent shape to the active-site cleft of the enzyme. This particular topology is perfectly adapted to the U-shaped conformation of laminarin chains in solution, and thus explains the predominant specificity of ZgLamAGH16 for this substrate (Labourel et al. 2014).

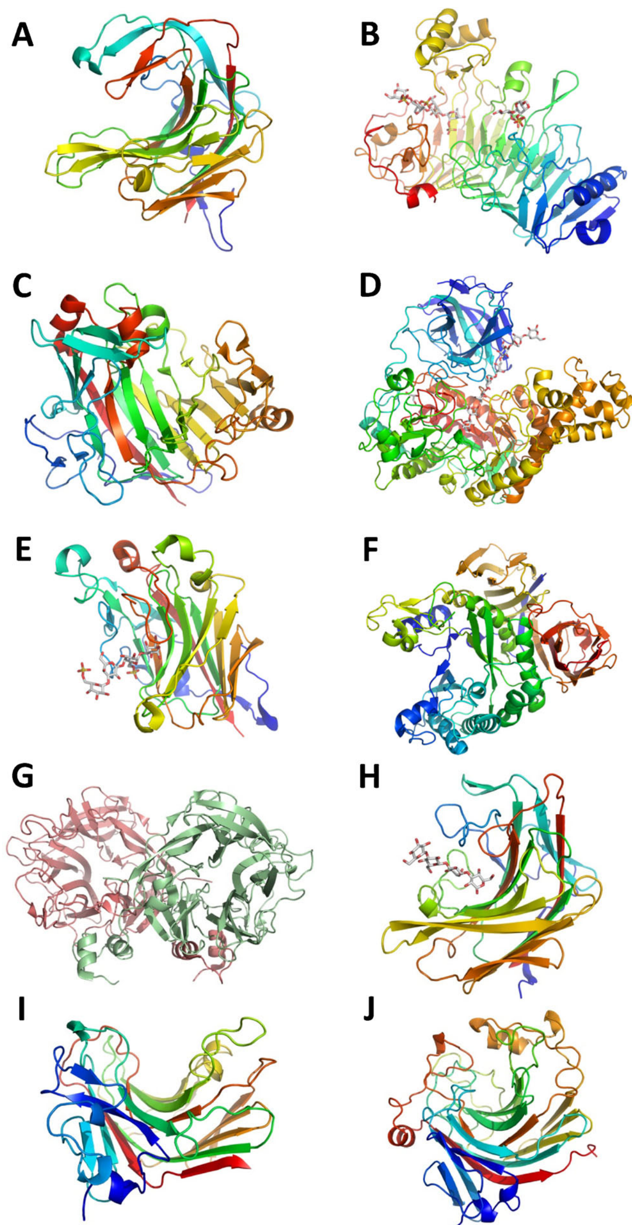

Fig. 1 Representative crystal structures of algal-specific polysaccharidases. Structure of the GH16 kappa-carrageenase from *P. carrageenovora* (**a**, PDB 1DYP), of the GH82 iota-carrageenase from *A. fortis* in complex with oligo-iota-carrageenans (**b**, PDB 1KTW), of the GH16 beta-agarase ZgAgaD from *Z. galactanivorans* (**c**, PDB 4ASM), of the GH50 exo-beta-agarase Aga50D from *S. degradans* in complex with an oligo-agar (**d**, PDB 4BQ5), of the GH16 beta-porphyranase ZgPorA from *Z. galactanivorans* in complex with an oligo-porphyran (**e**, PDB 3ILF), of the GH86 beta-porphyranase BpGH86A from *B. plebius* (**f**, PDB 4AW7), of the GH117 α-1,3-(3,6-anhydro)-L-galactosidase ZgAhgA from *Z. galactanivorans* (**g**, PDB 3P2N), of the GH16 laminarinase ZgLamA from *Z. galactanivorans* in complex with an oligo-laminarin (**h**, PDB 4BOW), of the PL7 endo-guluronate lyase ZgAlyA1 from *Z. galactanivorans* (**i**, PDB 3ZPY), and the PL7 exo alginate lyase ZgAlyA5 from *Z. galactanivorans* (**j**, PDB 3ZPY). The β-strands and the α-helices are represented by *arrows* and *ribbons*, respectively. The oligosaccharides are displayed with a stick representation. With the exception of ZgAhgA, all the structures are *colored with a rainbow spectrum* from the N (*blue*) to the C terminus (*red*). Chains A and B of ZgAhgA are *colored in pink and green*, respectively. This figure was prepared with the program Pymol

Ulvan lyases

Ulvans are the main cell wall components of green algae of the genus *Ulva* (Popper et al. 2011). These complex sulfated polysaccharides are composed mainly of sulfated L-rhamnose, D-glucuronic acid and its C5-epimer L-iduronic acid, and a minor fraction of D-xylose (Lahaye and Robic 2007). The first described ulvanolytic bacterium was isolated at a “green tide” site in the Saint-Brieuc Bay (Brittany). This bacterium was not further characterized, but a semi-purified enzyme was shown to cleave the β-(1,4) linkage between L-rhamnose-3-sulfate (Rha3S) and D-glucuronic acid (GlcA), releasing an oligosaccharide with an unsaturated uronic acid at the non-reducing end. This enzyme was thus a polysaccharide lyase, referred to as an ulvan lyase (Lahaye et al. 1997). The only ulvan lyase gene to have been cloned was obtained from *Persicivirga ulvanivorans* (Nyvall Collén et al. 2011), a flavobacterium isolated from the feces of the mollusk *Aplysia punctata* having fed on *Ulva* sp. (Barbeyron et al. 2011). This enzyme is endolytic and cleaves the glycosidic bond between the sulfated rhamnose and a glucuronic or iduronic acid. The sequence of this ulvan lyase has no similarity to known proteins (Nyvall Collén et al. 2011) and is currently an unclassified polysaccharide lyase in the CAZY database.

Microorganisms enhance algal defense, growth, and nutrient uptake

An increasing number of reviews discuss the beneficial contribution of microorganisms to algae, and notably their role in improving algal defense and nutrient uptake and in stimulating algal morphology and algal spore germination (Barott et al. 2011; Egan et al. 2013; Goecke et al. 2010; Harder et al. 2012). Alga-associated bacteria contribute to algal defense by producing antimicrobial and antifouling compounds (Wilson et al. 2011). Table 3 shows diverse algal species on which bacteria with antimicrobial activities have been identified. Some 27 % of isolated strains, on the average, show antimicrobial/antibacterial activity. The percentage is much lower for planktonic strains isolated from seawater (only 7 % show antimicrobial activity) and even lower in terrestrial samples (Penesyan et al. 2009). The most represented bacterial genera are *Bacillus*, *Pseudoalteromonas*, *Pseudomonas*, and *Streptomyces*. Gram-positive *Bacillus* and *Streptomyces* and gram-negative *Pseudomonas* and *Pseudoalteromonas* are genera known for their ability to produce bioactive compounds (Bhatnagar and Kim 2010).

Prokaryotes have also been observed to synthesize necessary vitamins (Croft et al. 2005, 2006) and growth factors (Dimitrieva et al. 2006; Tsavkelova et al. 2006) and to improve algal growth by making these compounds accessible in sufficient amount.

Lastly, microbial epibionts produce common hydrolytic enzymes that improve algal nutrient uptake and development. A bacterial strain isolated from the red alga *Sargassum serratifolium*, for example, was shown to contain, in addition to agarase activities, diverse other hydrolytic activities such as amylase, alkaline phosphatase, esterase, and lipase (C14), β-galactosidase, and urease activities (Kim and Hong 2012). In other bacterial strains also found on *Sargassum* sp., amylase, carboxymethylcellulase, and protease activities were found (Mohapatra and Bapuji 2003). An alkaline serine protease with potential use in the laundry industry was found in *Bacillus megaterium* RRM2, isolated from a red alga species (Rajkumar et al. 2011). Furthermore, bacterial enzymes such as lipases and esterases (Rajkumar et al. 2011), cellulases (Dong et al. 2010; Fu et al. 2010; Gibbs et al. 1992), proteases (Cristóbal et al. 2011; Yang et al. 2013), amylases (Both et al. 1993; Liu et al. 2012), laccases (Fang et al. 2012; Ge et al. 2011), and beta-glucosidases (Cristóbal et al. 2009; Mai et al. 2013), distantly related to terrestrial ones and displaying original biochemistry, are increasingly being isolated from the marine environment.

All these interesting bioactive compounds and enzymes produced by microorganisms in interaction with algae might predictably be very useful in diverse medical and industrial applications, as described in the next section.

Interest of macroalga-associated microorganisms in biotechnological applications

Medical and pharmaceutical applications

Microbial pathogens are becoming increasingly resistant to antibiotics, making some human infections untreatable. Hence, new antimicrobial compounds of natural origin, specifically targeting certain pathogens, are urgently needed. The marine environment is increasingly explored for such compounds. Although marine macroorganisms, including algae, are known to produce many interesting antimicrobial, antifungal, and potentially therapeutic compounds (Engel et al. 2002; Kubanek et al. 2003; Mayer and Gustafson 2003; Paul and Puglisi 2004; Steinberg and de Nys 2002; Takamatsu et al. 2003), ensuring a continued supply of eukaryotic compounds seems quite impossible. Producing such compounds would require growing macroorganisms in large quantity, and this would require much time and space (Dobretsov et al. 2006). Furthermore, the chemical synthesis of complex eukaryotic compounds is difficult. Therefore as microorganisms on algae release many bioactive compounds that prevent extensive colonization by other microorganisms, larvae, or algae, they could represent an interesting source of new antimicrobials (see Table 2), easily exploitable as they produce compounds faster in large quantity and are easier to culture. Moreover, marine microorganisms seem extremely productive of secondary metabolites: in addition to antimicrobial metabolites, they have been found to produce antitumor, anticancer, cytotoxic, and photoprotective compounds (Bhatnagar and Kim 2010). For example, it has recently been shown that phloroglucinol, a precursor of brown algal phlorotannins used in medicine to treat abdominal pain (Chassany et al. 2007), is synthesized by a polyketide synthase acquired through horizontal gene transfer from an ancestral actinobacterium (Meslet-Cladiere et al. 2013). This highlights the importance of bacterial epibionts both in algal evolution and as a source of interesting bioactive compounds (Meslet-Cladiere et al 2013). Lastly, algal-polysaccharide-degrading enzymes have a wide range of medical and pharmaceutical applications because they produce remarkable biologically active oligosaccharides with properties useful in maintaining human health, such as anticoagulant (Pereira et al. 1999; Pushpamali et al. 2008), anti-inflammatory (Berteau and Mulloy 2003), antioxidant (Hatada et al. 2006; Jiao et al. 2012), or immunostimulating activity (Bhattacharyya et al. 2010). Furthermore, oligosaccharides derived from ulvans, agars, carrageenans, alginates, and other less known algal polysaccharides are explored for their potential use as prebiotics favoring gut health in humans and animals (O'Sullivan et al. 2010). To obtain active oligosaccharides with the desired properties, enzymatic production with specific algal-polysaccharide-degrading enzymes is required. As microorganisms on algae are main producers of such specific enzymes, they represent a great source of them.

Production of biofuels

The need to preserve fossil fuels has prompted increasing efforts to produce biofuels. Initial efforts focused on producing biofuels from plant biomass. Unfortunately, using this biomass requires complex extraction methods due to the presence of recalcitrant polysaccharides such as lignocellulose. Furthermore, to obtain plant biomass one needs land for cultivation, in competition with human and animal food. Therefore, non-lignocellulosic macroalgal biomass, requiring no land for cultivation and possessing a high carbohydrate content, seems an interesting alternative for biofuel production. Promising results have been obtained in studies aiming to produce bioethanol from brown algae (Enquist-Newman et al. 2013; Wargacki et al. 2012) or red algae (Kim et al. 2012). All of these studies used microbial enzymes, directly or indirectly, to degrade specific algal polysaccharides. For example, Wargacki et al. (2012) used *E. coli* strains transformed with DNA encoding enzymes involved in alginate transport and metabolism, in combination with an extracellular depolymerization system, to metabolize alginate and synthesize ethanol. Kim et al. (2012) used several microbial agarases to saccharify agarose to monosugars for further fermentation to ethanol. Lastly, the very recent study of Enquist-Newman et al. (2013) used bacterial alginate and mannitol

Table 3 Percentages and genera of bacterial strains exhibiting antimicrobial activities, isolated on seaweeds

Algae phyla	Algae species	% of isolated strains with antimicrobial activities (total isolated strains)	Bacteria genera identified with antimicrobial activities	Source
Phaeophyta	*Laminaria saccharina*	49 % (210)	*Bacillus*, *Glaciecola*, *Kopriimonas*, *Mesorhizobium*, *Pseudoalteromonas*, *Streptomyces*,	(Wiese et al. 2009)
	Pelvetia canaliculata	7 % (55)	*Alteromonas*, *Pseudomonas*	(Lemos et al. 1985)
	Fucus ceranoides	13 % (45)		
	Fucus vesiculosus	53 % (69)	*Bacillus*, *Parracoccus*, *Pseudomonas*, *Streptomyces*	(Goecke et al. 2013)
	Sargassum serratifolium	20 % (116)	*Bacillus*	(Kanagasabhapathy et al. 2006)
	Sargassum fusiforme			
	Sargassum filicinum			
	Padina arborescens			
	Undaria pinnatifida Petalonia fascia			
	Colpomenia sinuosa Scytosiphon lomentaria			
	Ecklonia cava			
Rodophyta	*Delesseria sanguine*	51 % (97)	*Algoriphagus*, *Microbacterium*, *Paenibacillus*, *Pseudoalteromonas*, *Streptomyces*, *Zobellia*	(Goecke et al. 2013)
	Jania rubens	36 % (19)	*Aquamarina*, *Bacillus*, *Paracoccus*, *Pseudoalteromonas*, *Pseudomonas*	(Ismail-Ben Ali et al. 2011)
	Pachymeniopsis lauceola, *Plocamium telfairiae*	33 % (92)	*Bacillus*, *Microbacterium*, *Psychrobacter*, *Vibrio*	(Kanagasabhapathy et al. 2008)
	Gelidium amansii			
	Chondrus oncellatus			
	Grateloupia filicina			
	Ceramium kondoi			
	Lomentaria catenata			
	Schizymenia dubyi Porphyra yezoensis			
	Delisea pulchra	12 % (325)	*Micrococcus*, *Phaeobacter*, *Pseudoaltermonas*, *Rhodobacteraceae*, *Roseobacter*, *Ruegeri*, *Schwenalla*, *Vibrio*	(Penesyan et al. 2009)
Chlorophyta	*Ulva australis*	12 % (325)	*Bacillus*, *Flavobacteriaceae*, *Phaeobacter*, *Photobacterium*, *Roseobacter*	(Penesyan et al. 2009)
	Enteromorpha intestinalis	34 % (46)	*Alteromonas*, *Pseudomonas*	(Lemos et al. 1985)
	Enteromorpha compressa	18 % (33)		
	Ulva lactuca	13 % (45)		

catabolism genes in *Saccharomyces cerevisiae* to metabolize alginate monomers (4-deoxy-L-erythro-5-hexoseulose uronates) and mannitol from brown seaweeds, for further fermentation of sugar to ethanol. These recent promising works demonstrate the advantage of identifying algal polysaccharide-degrading enzymes and the encoding genes for the production of green energy.

Industrial applications

The diversity of non-lignocellulosic, sulfated poly- and monosaccharides makes algal hydrocarbons interesting for diverse industrial and biotechnological applications (see Table 4). The most used and studied alga-specific polysaccharides are agars and carrageenans (red algae), ulvans (green algae), alginates, laminarin, and sulfated fucoidans (brown algae) (Popper et al. 2011). Polysaccharide biotechnology uses enzymes or enzyme systems to convert carbohydrate polymers to added-value new polysaccharides (De Ruiter and Rudolph 1997) and thus requires hydrolytic enzymes such as agarases, carrageenases, alginate lyases, fucoidanases, porphyranases, and sulfatases to modify useful algal polysaccharides, improve their structures, and enhance their functionalities. Moreover, enzymatic hydrolysis is increasingly viewed as a promising alternative to current chemical extraction methods (Gavrilescu and Chisti 2005). Therefore, industrialists also seek hydrolytic enzymes with commonly exploited activities, e.g., proteases, cellulases, amylases, beta-glucosidases, and laccases, but with original properties making them suitable for new applications. To date, most enzymes used in industry have been isolated from microorganisms living in terrestrial environments, mainly soils. Marine microorganisms, being exposed to extreme temperature, pressure, salinity, and nutrient availability conditions, should provide new enzymes with original biochemistry and characteristics (Kennedy et al. 2011). Lastly, alga-associated microbial communities respond to their exposure to alga-derived metabolites by producing a range of specific compounds, potentially of biotechnological interest. For example, various industries use halogenated compounds that become a hazard when they end up in the environment. Many studies therefore focus on optimizing their biodegradation by microbial dehalogenases (Swanson 1999). Alga-associated microorganisms constitute a potential source of dehalogenases, as they appear to resist the halogenated metabolites that algae produce as a defense mechanism (Potin et al. 1999).

Table 4 Industrial applications using algal polysaccharides

Industrial domain	Industrial use	Algal polysaccharides	Source
Pharmacy	Laxative Toothpaste	Agars Carrageenans	(Bixler and Porse 2010; Jiao et al. 2011; Jung et al. 2013; Li et al. 2008; McHugh 2003)
	Therapeutic peptides	Carrageenans, fucoidans	
	Pharamaceutical tablet desintegrant	Alginates	
	Medical fiber	Alginates	
	Wound dressing	Alginates	
	Controlled release of medical drugs and other chemicals	Alginates	
	Dietary food	Alginates, carrageenans	
Food industry	Gelling properties Stabilizer	Agars, carrageenans Agars, alginates	(McHugh 2003)
	Thickener	Agars, alginates	
	Meat substitute	Agars	
	Wine clarification	Agars	
	Prevent pulp precipitation in fruit juices	Alginates	
	Conservation of frozen fish	Alginates	
Laboratory	Bacterial growth	Agar	(McHugh 2003)
Phytopharmacie	Activate signal pathway in plants and enhance their immune system	Alginates, carrageenans, fucans, laminarin, ulvan	(Vera et al. 2011)
Paper industry	Smooth paper	Alginates	(McHugh 2003)
Textile industry	Thickeners for the paste containing the dye	Alginates	(McHugh 2003)
Biofuel	Biogas, bioethanol, biobutanol	Alginate, laminarin, mannitol	(Jung et al. 2013; Wargacki et al. 2012)
Other industry	Welding rod Immobilized biocatalyst	Alginates Alginates	(McHugh 2003)

Prospects for exploiting algal epibionts

As shown in the first part of this review, microorganisms living on algae are highly diverse but underexplored. The composition of alga-associated microbial communities varies, for example, according to the alga phylum and species, the season, and the age of the thalli. Furthermore, as these microorganisms constantly metabolize algal products, they produce numerous specific enzymes and secondary metabolites. From their immense diversity and their constant activity stems their great potential as a source of novel and original enzymes and metabolites. Furthermore, specific hydrolytic enzymes with novel biochemistry are increasingly sought for biotechnological applications in biomass and biofuel production, medicine, and wide-ranging industrial applications. Algal polysaccharidases identified to date (such as agarases, carrageenases, and alginate lyases) display very specific structures and biochemistry, related only distantly to those of known terrestrial glycoside hydrolases. This highlights their huge potential for new and original biotechnological uses and the importance of investigating these interesting enzymes.

Most published investigations on algal epibionts and their metabolites have relied on cultivation methods. To our knowledge, indeed, all specific enzymes isolated from algal epibionts have been obtained from cultivable microbial strains. Some high-throughput screens of algal microbial communities have been performed, but functional metagenomics has not been used to identify new microbial enzymes and metabolites. Functional metagenomics and techniques such as high-throughput sequencing are powerful means of gaining knowledge on the microorganisms composing these underexplored communities and of identifying novel metabolites and specific enzymes produced by alga-associated microbes.

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