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Minireview

Recent insights into oceanic dimethylsulfoniopropionate biosynthesis and catabolism

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Summary

Dimethylsulfoniopropionate (DMSP), a globally important organosulfur compound is produced in prodigious amounts (2.0 Pg sulfur) annually in the marine environment by phytoplankton, macroalgae, heterotrophic bacteria, some corals and certain higher plants. It is an important marine osmolyte and a major precursor molecule for the production of climate-active volatile gas dimethyl sulfide (DMS). DMSP synthesis take place via three pathways: a transamination 'pathway-' in some marine bacteria and algae, a Met-methylation 'pathway-' in angiosperms and bacteria and a decarboxylation 'pathway-' in the dinoflagellate, *Crypthecodinium*. The enzymes DSYB and TpMMT are involved in the DMSP biosynthesis in eukaryotes while marine heterotrophic bacteria engage key enzymes such as DsyB and MmtN. Several marine bacterial communities import DMSP and degrade it via cleavage or demethylation pathways or oxidation pathway, thereby generating DMS, methanethiol, and dimethylsulfoxonium propionate, respectively. DMSP is cleaved through diverse DMSP lyase enzymes in bacteria and via Alma1 enzyme in phytoplankton. The demethylation pathway involves four different enzymes, namely DmdA, DmdB, DmdC and DmdD/AcuH. However, enzymes involved in the oxidation pathway have not been yet identified. We reviewed the recent advances on the synthesis and catabolism of DMSP and enzymes that are involved in these processes.

Introduction

In the marine environment, the tertiary sulfonium compound dimethylsulfoniopropionate (DMSP) is produced in enormous amounts (2.0 Pg sulfur) annually (Hatton *et al*., 2012; Galí *et al*., 2015; Ksionzek *et al*., 2016), by many microalgae such as coccolithophores, dinoflagellates and diatoms (Curson *et al*., 2018; Kageyama *et al*., 2018), macroalgae the red algae *Polysiphonia* (Reed, 1983), corals such as *Acropora* sp. (Raina *et al*., 2013), coastal angiosperms such as *Spartina alterniflora* (Kocsis *et al*., 1998) and *Wollastonia biflora* (Hanson *et al*., 1994), heterotrophic bacteria such as *Labrenzia aggregata* (Curson *et al*., 2017) and non-marine higher plants such as sugarcane (Paquet *et al*., 1994). It has been proposed that DMSP in the 'producer organism' can function as an osmolyte (Vairavamurthy *et al*., 1985; Kirst, 1990), predator deterrent (Wolfe and Steinke, 1996), protectant against hydrostatic pressure (Zheng *et al*., 2020), chemical signalling molecule (Seyedsayamdost *et al*., 2011; Johnson *et al*., 2016), chemoattractant (Miller *et al*., 2004; DeBose *et al*., 2008; Seymour *et al*., 2010), antioxidant (Sunda *et al*., 2002; Lesser, 2006; Husband *et al*., 2012), cryoprotectant (Karsten *et al*., 1996) and/or sink for excess sulfur and carbon (Stefels, 2000) and a precursor of malleicyprols (Trottmann *et al*., 2020). The particulate DMSP levels can range from nanomolar to micromolar concentrations in surface water during phytoplankton blooms a (Yoch, 2002; Speeckaert *et al*., 2018). It has been reported that massive bloom of the dinoflagellate *Akashiwo sanguinea* that occurred in Monterey Bay, CA, USA, in the fall of 2016 led to exceptionally high seawater DMSP concentrations that peaked at 4240 nM (Kiene *et al*., 2019). DMSP synthesis from methionine (Met) in various organisms has been shown to take place via three pathways: a transamination 'pathway-' in some marine bacteria and algae (Curson *et al*., 2017; Curson

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et al., 2018), a Met methylation 'pathway-' in angiosperms and bacteria (Otte *et al*., 2004; Lyon *et al*., 2011; Williams *et al*., 2019) and a decarboxylation 'pathway-' in the dinoflagellate, *Crypthecodinium* (Uchida *et al*., 1996). The genes involved in DMSP biosynthesis such as *dsyB* in bacteria (Curson *et al*., 2017), *DSYB* in algae (Curson *et al*., 2018) and *TpMMT* in the diatom *Thalassiosira pseudonana* (Kageyama *et al*., 2018) encode the key methylthiohydroxybutyrate *S*-methyltransferase enzyme of the Met transamination pathway, while *mmtN* in bacteria encodes the key Met methyltransferase of the Met methylation pathway (Williams *et al*., 2019). So far, there is no report on enzymes involved in the Met decarboxylation pathway. Recent identification of DMSP biosynthesis gene in bacteria and algae will greatly enhance our understanding to model and monitor DMSP production. The percentage of DMSP-producing bacteria estimated from metagenomes derived from marine sediments is approximately 1.1%, which, when applied to the estimated 1.99×10^{10} bacterial cells g^{-1} of marine surface sediment, suggests an abundance of around 1×10^{8}DMSP-producing bacteria g^{-1} of sediment (Williams *et al*., 2019). DMSP-producing bacteria represent 0.3%–0.6% of a reported 1×10^{6} bacteria ml^{-1} in seawater. Thus, bacteria are reported as key DMSP producers within these sediments (Williams *et al*., 2019). It has been observed that algal *DSYB* transcripts are approximately twofold more abundant than that of the bacterial *dsyB* gene in North Pacific Ocean metatranscriptome study, which supports algae as the major contributors to DMSP production in photic seawater (Curson *et al*., 2018). DMSP once released into the environment through grazing and/or virus-induced lysis provides nutrients for marine microorganisms in the form of carbon, sulfur and/or energy (Curson *et al*., 2011a). DMSP produced by phytoplankton may account for 10% of the total carbon fixation in parts of the ocean (Archer *et al*., 2001; Simó *et al*., 2002) and it can account for up to 71% of the sulfur and 15% of the cells carbon demand in DMSP-producing phytoplankton (Matrai and Keller, 1994; Simó *et al*., 2002). DMSP supports 1%–13% of the carbon demand for the bacteria in surface seawater (Kiene and Linn, 2000) and is a key source of reduced sulfur for the growth of heterotrophic bacteria such as SAR11 (Tripp *et al*., 2008). Marine heterotrophic bacteria, notably Roseobacter (*Roseobacteraceae*) and SAR11, are the major contributors to global DMSP catabolism (Curson *et al*., 2011a; Sun *et al*., 2016; Liang *et al*., 2021), in addition to many marine phytoplankton (Stefels, 2000; Alcolombri *et al*., 2015) and some fungi (Todd *et al*., 2009; Kirkwood *et al*., 2010b). A broad range of microorganisms transport DMSP from seawater (Malmstrom *et al*., 2004; Vila *et al*., 2004; Howard *et al*., 2008; Raina *et al*., 2017) and catabolize it through three pathways: demethylation, cleavage and recently reported oxidation pathway (Curson *et al*., 2011a; Moran *et al*., 2012; Sun *et al*., 2016; Thume *et al*., 2018). During demethylation, a series of 'Dmd' enzymes generate acetaldehyde and methanethiol (MeSH) from DMSP and provide the microbial food web with organic carbon and reduced sulfur (Reisch *et al*., 2011b; Moran *et al*., 2012). It is estimated that 80% of DMSP degrades through demethylation (Curson *et al*., 2011a). DMSP demethylation in bacteria involves four different enzymes, namely DmdA, DmdB, DmdC and DmdD/AcuH (Howard *et al*., 2006; Reisch *et al*., 2011b). It is reported that only a minor fraction of dissolved DMSP in seawater, ranging between 2% and 21%, is enzymatically cleaved to generate climate-active gas DMS (Kiene and Linn, 2000), which is a major natural source of volatile organic sulfur compound in the atmosphere (Charlson *et al*., 1987; Andreae, 1990; Simó, 2001; Stefels *et al*., 2007). DMSP cleavage includes eight different DMSP lyases, namely DddD, DddP, DddQ, DddK, DddL, DddX, DddY and DddW, in bacteria that work independently from each other and an Alma1 in phytoplankton (Alcolombri *et al*., 2015; Johnston *et al*., 2016; Sun *et al*., 2016; Li *et al*., 2021). Approximately 300 teragrams (Tg) of DMS is produced each year mainly by the DMSP cleavage pathway through several DMSP lyases, of which 13–37 Tg is transferred into the atmosphere through ocean–atmosphere sulfur flux (Curson *et al*., 2011a; Johnston *et al*., 2016; Ksionzek *et al*., 2016). DMS in the atmosphere is photochemically oxidized to dimethyl sulfoxide (DMSO) or sulfate aerosols, which act as cloud condensation nuclei (CCN), leading to increased albedo effect (the amount of sunlight reflected back into space) (Vallina and Simo, 2007; Curson *et al*., 2011a). It has also been theorized that their albedo effect is part of a feedback loop controlling local climate, termed the CLAW hypothesis after the authors who first postulated it (Charlson *et al*., 1987). This feedback loop was suggested because it had already been established that DMS is one of the major sources of CCN, and therefore the formation of clouds could be regulated by controlling the release and oxidation of DMS (Charlson *et al*., 1987). Blooms of phytoplankton were found to produce higher amounts of DMS in warmer conditions (Charlson *et al*., 1987), likely because increased solar radiation leads to better growth (Schäfer *et al*., 2010). Higher DMS means increased CCN and therefore cloud formation, reflecting radiation away from the surface and cooling it, which then leads to a decrease in growth and production, causing the cloud cover to ease off and allow more radiation again, maintaining balance (Schäfer *et al*., 2010). This theory, while often referenced, has not been fully

validated, and even though there is evidence for levels of DMS being driven by light dosage (Vallina and Simó, 2007), it is now widely thought to be unlikely, or at the very least more complex than previously suggested (Quinn and Bates, 2011), namely due to the existence of other sources of CCN that are not DMS derived. In the oxidation pathway, DMSP is also oxidized to dimethylsulfoxonium propionate (DMSOP) in eukaryotic microalgae and in bacteria. Certain bacteria such as *Sulfitobacter sp*., *Ruegeria pomeroyi*, *A. faecalis* and *Halomonas* sp. metabolize DMSOP and therefore contribute to the marine DMSO pool. However, enzymes involved in the oxidation pathway have not been yet identified (Thume *et al*., 2018).

DMSP biosynthesis and catabolism in different oceanic regions

Studies on the bacterial DMSP-degrading genes such as *dmdA* and *dddP* have been carried out in varied marine environments (Cui *et al*., 2015; Kuek *et al*., 2016; Zeng *et al*., 2016; Liu *et al*., 2018; Nowinski *et al*., 2019; Cui *et al*., 2020; Teng *et al*., 2021) and reported that these genes are taxonomically diverse and widespread across almost all major oceans, from tropical waters to the polar sea (Peng *et al*., 2012; Cui *et al*., 2015; Zeng *et al*., 2016; Teng *et al*., 2021). In comparison to DMSP catabolism, there were few molecular studies on environmental DMSP production and these showed bacterial DMSP production to be significant in surface coastal sediment, marine sediment and seawater, sea surface microlayer, estuary, and deep-ocean environments (Williams *et al*., 2019; Song *et al*., 2020; Sun *et al*., 2020; Zheng *et al*., 2020; Sun *et al*., 2021; Zhang *et al*., 2021). Several amplicon-, metagenomic- and metatranscriptomic-based studies on DMSP biosynthesis and catabolism have been summarized in Table 1.

Biosynthesis of DMSP

Here, DMSP production in algae, bacteria, plants and animals, including corals is reviewed (Reed, 1983; Keller *et al*., 1989; Hanson *et al*., 1994; Paquet *et al*., 1994; Kocsis *et al*., 1998; Otte *et al*., 2004; Raina *et al*., 2013; Ausma *et al*., 2017; Curson *et al*., 2017; Curson *et al*., 2018; Kageyama *et al*., 2018; Williams *et al*., 2019).

DMSP synthesis in bacteria. A wide diversity of marine heterotrophic bacteria are reported to synthesize DMSP by the Met transamination pathway described previously in macroalgae and phytoplankton (Gage *et al*., 1997; Curson *et al*., 2017; Curson *et al*., 2018) and Met methylation pathway (Liao and Seebeck, 2019) (Fig. 2). DsyB protein (encoded by *dsyB* gene), an important enzyme for DMSP production, was first identified in marine Alphaproteobacteria – *Labrenzia aggregata* LZB033 reported from the East China Sea (Curson *et al*., 2017). The DsyB proteins are found to be functional in *L. aggregata* IAM12614, *Amorphus coralli* DSM19760, *Pelagibaca bermudensis* HTCC260 and *Oceanicola batsensis* HTCC2597. *L. aggregata* LZB033 is reported to produce 99.8 pmol DMSP μg^{-1} protein having an intracellular concentration of 9.6 mM (Table 2). In *L. aggregata* LZB033, DMSP production and *dsyB* transcription levels are enhanced with increasing salinity, decreasing nitrogen, decreasing temperature and also in stationary phase. However, there was no detrimental effect on the growth of *Labrenzia dsyB*$^{-}$ mutant J571 under saline conditions. While *Labrenzia dsyB*$^{-}$ mutant showed enhanced levels of the nitrogenous osmolyte glycine betaine (GBT) production compared with the wild type, which compensates for the loss of DMSP (Curson *et al*., 2017). *De novo* DMSP synthesis does not appear to have a key role in osmoprotection. The phylogenetic relation among bacterial genera with DsyB proteins are illustrated in Fig. 2. Another key enzyme involved in DMSP biosynthesis was identified as MmtN (encoded by *mmtN* gene) in *Novosphingobium* BW1 and reported to confer Met methyltransferase activity (MMT) (EC2.1.1.12), converting Met to *S*-methyl-methionine (SMM). MmtN homologues with ≥54% amino acid identity were identified in many marine Alphaproteobacteria, Gammaproteobacteria and some Actinobacteria (Williams *et al*., 2019). The complete description of a DMSP biosynthetic pathway by *in vitro* reconstitution from *Streptomyces mobaraensis* had been recently reported (Fig. 1) and MmtN from *S. mobaraensis* showed MMT activity (Liao and Seebeck, 2019). MmtN proteins are shown to be functional in *Thalassospira profundimaris* WP0211, *Novosphingobium* sp. MBES04, *S. mobaraensis* NBRC13819, *Nocardiopsis chromatogenes* YIM90109 and *Roseovarius indicus* B018. The phylogenetic relation among bacteria with MmtN proteins are depicted (Fig. S1). *Thalassospira profundimaris mmtN*$^{-}$ mutant showed no significant growth reduction compared with the wild-type strain under increased salinity and/or reduced nitrogen concentrations, known to enhance DMSP production. The *T. profundimaris mmtN*$^{-}$ mutant produced high levels of GBT compared with the wild type. Bacteria harbouring functional MmtN proteins are not monophyletic, suggesting that mmtN may have been horizontally transferred between these microorganisms (Williams *et al*., 2019). Recently, DMSP biosynthesis in *Burkholderia thailandensis* has been reported (Trottmann *et al*., 2020). By analogy to one of the established bacterial DMSP biosynthesis pathways, methionine undergoes *S*-methylation to form *S*-methylmethionine, decarboxylation, transamination and

Table 1. Amplicon, metagenomic and metatranscriptomic based studies.

Regions	DMSP biosynthesis	DMSP cleavage	References
Mariana Trench, Yarmouth estuary and Stiffkey saltmarshes	The metagenomic analysis predicted that approximately 1% of bacteria contain *dsyB* in surface sediment samples obtained from Stiffkey saltmarshes. Bacteria containing *mmtN* were much less abundant than those with *dsyB* in tested seawater. DMSP-producing bacteria were much less abundant in the Ocean Microbial Reference Gene Catalogue Metagenomic Database (OM-RGC; mostly surface seawater samples) and in tested coastal seawater samples. They represented 0.3%–0.6% of a reported 1×10^6 bacteria ml^{-1} in seawater. *dsyB* transcription was more than three orders of magnitude higher, per unit mass, in surface sediment than in surface seawater. *dsyB* and *mmtN* transcripts were ubiquitous or mostly present, respectively, at varying levels in Tara Oceans bacterioplankton metatranscriptome databases. The plastid 16S rRNA gene sequences of DMSP-producing eukaryotes belonged to *Asterionellopsis* (6%), *Phaeodactylum* (0.4%), and *Thalassiosira* (0.3%). In Stiffkey metagenomes the eukaryotic DMSP synthesis gene *DSYB* was approximately 13-fold less abundant than *dsyB*. Taxonomic profiling of the 16S rRNA gene amplicon sequencing from natural Stiffkey saltmarsh surface sediment revealed DMSP producing members at class level (*Alphaproteobacteria*, *Gammaproteobacteria*, *Deltaproteobacteria*, and *Actinobacteria*). Species-level phylogenetic analysis of the metagenomes from Stiffkey saltmarsh surface sediment indicated DMSP producing bacteria. The genera/species that contain *mmtN* (*Alteromonas sp*. N2, *Thalassospira profundimaris*, *Alteromonas* unclassified, *Thalassospira* unclassified, *Thalassospira lucentensis*), *dsyB* (*Ruegeria mobilis*, *Labrenzia alexandrii*, *Oceanicola* unclassified, *Labrenzia aggregata*), both *mmtN* and *dsyB* (*Labrenzia* unclassified), and those which contain representatives that produce DMSP with unknown DMSP synthesis genes (*Celeribacter baekdonensis*, *Marinobacter* unclassified, *Marinobacter adhaerens*)	In surface saltmarsh sediments, DddD, DddL and DddP present in 1.1%, 4.8% and 6.6% of bacteria, respectively	Williams *et al*. (2019)
Challenger Deep of the Mariana Trench	DMSP-producing bacteria (containing *dsyB* and/or *mmtN*) were far higher in deeper waters (≥4000 m; ∼2.58%–5.25%) than in surface waters (∼0.90%–1.18%). Bacteria with *mmtN* were always less abundant than those with *dsyB* in seawater metagenomes. The metagenomic *dsyB* sequences, including 37/162 metagenome-assembled genomes (MAGs), were Alphaproteobacterial, mainly *Rhodobacterales*, *Rhizobiales*, and *Rhodospirillales*. The majority of *mmtN* homologues were also *Alphaproteobacteria*, belonging to bacterial genera known to produce DMSP: *Thalassospira*, *Roseovarius*, *Labrenzia*, and *Novosphingobium. dsyB* and *mmtN* transcript abundances were far higher in all sediments than in water samples. *DSYB* and *TpMMT* genes were not detected in any trench samples	DMSP demethylation (via *dmdA*) was likely the dominant process in the surface waters. *dddP* was the most abundant DMSP lyase gene in the surface waters (∼6.48%). The *dddK*, *dddW*, and *dddY* genes were only predicted to be in 0%–0.26% of the seawater bacteria. *dddP* was found in 43% of MAGs (69), predicted to be *Alphaproteobacteria*, *Gammaproteobacteria*, *Acidimicrobiia*, *Bacteroidia*, SAR324, *Nitrososphaeria*, and *Anaerolineae*. Of 162 MAGs, 58 contained *dmdA*, likely from *Alphaproteobacteria*, *Gammaproteobacteria*,	Zheng *et al*. (2020)

(Continues)

Table 1. Continued

Regions	DMSP biosynthesis	DMSP cleavage	References
		Acidimicrobiia, SAR324, and *Nitrososphaeria*. *dmdA* was still the dominant gene in aphotic 2000–8000 m deep waters, predicted to be present in 5.43%–26.66% of bacteria, but its relative abundance decreased with depth. Interestingly, the relative abundance of bacteria with DMSP lyases significantly increased in these deeper waters (2000–8000 m), with cumulatively more *ddd* genes observed in metagenomes from 4000 m to the trench bottom, compared to *dmdA*. DddP was still the predominant DMSP lyase in the 2000–8000 m deep waters (averaging 4.84%), but DddQ (up to 3.55%), DddL (up to 4.61%), and DddD (up to 1.61%) were better represented in these waters compared to the surface waters. Seawater DddQ sequences were most similar to those in the *Rhodobacteraceae*, including *Ruegeria*, *Leisingera*, and *Roseovarius*. DddL sequences were homologous to *Gammaproteobacteria*, represented by *Marinobacter*. In comparison, the DddD homologues differed through the water column, with surface waters containing *Alphaproteobacterial Sagittula* homologues, and *Gammaproteobacterial Halomonas* homologues being predominant in 8000 m samples. The algal DMSP lyase *Alma1* was not present in any trench samples	
Eastern China marginal seas (including the Bohai Sea, the Yellow Sea, and the East China Sea) and hydrothermal field of Okinawa Trough	Bacterial genetic potential to make DMSP was far higher than for phytoplankton in all samples, but particularly in the sediment where no algal DMSP synthesis genes were identified. The dominant seawater *dsyB* genes in metagenome-assembled genomes (MAGs) were from *Alphaproteobacterial Roseospirillum* and *Thalassobaculum* bacteria. Different bacterial *dsyB* genes, clustering with those from *Pseudooceanicola*, *Roseovarius*, and *Roseospirillum*, dominated in the Bohai Sea and Yellow Sea sediments (BYSS) sediment. The	DMSP catabolic pathways mediated by the DMSP lyase DddP and DMSP demethylase DmdA enzymes and MddA-mediated MeSH *S*-methylation were very abundant in BYSS samples. However, the genetic potential for DMSP degradation was very low in	Song *et al*. (2020) and Sun *et al*. (2020)

(Continues)

Table 1. Continued

Regions	DMSP biosynthesis	DMSP cleavage	References
	potential DMSP-producing bacteria dominating the Okinawa Trough hydrothermal field sediment were also distinct with their *dsyB* genes predicted to be in *Caenispirillum*, *Albimonas*, and *Oceanicola* bacteria. The bacterial *mmtN* gene was absent in all of the metagenome sequences in the tested environment. The algal *DSYB* gene was present at similar levels (0.2%–0.6% of eukaryotes) in the surface and bottom seawater samples but was not found in the BYSS or hydrothermal sediment metagenomes. In the East China Sea, DMSP-producing bacteria were more abundant in sea surface microlayer (SML) than subsurface seawater (SSW) samples, confirmed by the higher *dsyB* (∼7-fold) and *mmtN* (∼4-fold) gene abundances in the SML samples. Furthermore, SML samples possessed ∼3-fold higher *dsyB* transcripts than those from SSW. *mmtN* transcripts were also detected in the sample but these were more evenly distributed between SML and SSW samples. *Alteromonas*, *Ruegeria*, *Roseovarius*, *Hoeflea*, *Thalassospira*, *Labrenzia*, and *Novosphingobium* that can contain *dsyB* and/or *mmtN* genes were significantly more abundant in SML compared with SSW samples. Bacterial genera are known to produce/potential DMSP, e.g., *Pseudoalteromonas* and *Marinobacter*, were also more abundant in SML than in SSW and potentially contribute to the DMSP produced	the hydrothermal sediment samples – *dddP* was the only catabolic gene detected and in only one sample. The *dmdA* gene was mostly in SAR11, SAR116 (*Candidatus Puniceispirillum*), and *Rhodobacterales* bacteria in both seawater and sediment. The *ddd* genes were largely in SAR11 and *Rhodobacteraceae* in seawater, whereas they were mainly in *Alphaproteobacterial Rhizobiales* and *Rhodobacterales* bacteria as well as *Gammaproteobacterial Pseudomonadales* bacteria in the sediment. Most DMSP catabolic genes, like *dmdA*, were not identified in the majority of hydrothermal samples. Only one *dddP* sequence was detected in an Iheya ridge sample. In the East China Sea, DMSP demethylase gene *dmdA* (sum of C/2 and D/1) especially its C/2 subclade was significantly more abundant in the SML (∼ 1.5-fold and ∼ 3.2-fold) compared with SSW samples. Consistently, their transcripts were also more abundant (∼6.6-fold for *dmdA* and ∼8.2-fold for C/2) in SML compared with SSW samples. In contrast, there were no significant differences in *dddP* abundance or its transcript levels between the SML and SSW samples	
South China Sea (SCS)	*dsyB* was predicted to be in 0.0007%–0.0195% of sediment bacteria. The abundance of these bacteria increased when samples were incubated under conditions known to enrich for DMSP-producing bacteria. 16S rRNA gene amplicon sequencing revealed that the relative abundance of DMSP-producing bacteria was higher in the 30-, 50-, 90-, and 390-cm samples than those from surface sediment but was extremely low at the 690-cm samples. *Oceanospirillum*, *Thalassospira*, *Marinobacter*, and *Rhodobacteraceae* species were dominant predicted DMSP-producing bacteria in the SCS subseafloor. The metagenomic data revealed that *dsyB* was the dominant DMSP synthesis gene in the enriched samples of surface sediment. In contrast, the metagenomics data suggested *mmtN* as the predominant DMSP biosynthesis gene in the enriched subseafloor	Bacterial DMSP catabolic genes were also most abundant in the SCS surface sediments with high DMSP concentrations	Zhang *et al*. (2021)

(Continues)

Table 1. Continued

Regions	DMSP biosynthesis	DMSP cleavage	References
	sediment samples (50, 90, and 390 cm) than in the surface samples. The metagenomic MmtN sequences belonged to *Thalassospira* species, and DsyB sequences closely resembled sequences from *Rhodobacteraceae* including *Phaeobacter*, *Stappia*, *Pseudooceanicola*, and *Salipiger*. In addition, novel DMSP-producing bacterial isolates with unknown DMSP biosynthesis genes were identified in the SCS sediments, such as *Marinobacter* (*Gammaproteobacteria*) and *Erythrobacter*(*Alphaproteobaceria*)		
Arctic and Antarctic	Bacterial DMSP biosynthesis pathway (e.g. *dsyB*, *mmtN*) was not predominant in 60 metagenomic samples from polar waters	Bacteria mediated DMS/DMSP cycling was investigated in 60 seawater metagenomes and 214 MAGs obtained from polar oceans. There appeared to be an intense DMS/DMSP cycle in polar oceans. *dmdA*, *dddD*, *dddP*, and *dddK* were the most prevalent bacterial genes involved in DMS/DMSP cycling. *Alphaproteobacteria* and *Gammaproteobacteria* seemed to play prominent roles in DMS/DMSP cycling in polar oceans	Teng *et al*. (2021)
Changjiang Estuary	The abundance of bacterial DMSP producers and their *dsyB* and *mmtN* transcripts were lowest in the freshwater samples and increased abruptly with salinity in the transitional and seawater samples. The 16S rRNA amplicon analysis showed that *Alteromonas*, *Roseovarius*, *Thiobacimonas* (*Salipiger*), and *Marinobacter* were the major observed bacterial genera predicted to produce DMSP, as well the *Nisaea* in winter samples. Metagenomics analysis suggested that bacterial DMSP-producers were more abundant than their algal equivalents and were more prominent in summer than winter samples. Metagenomics analysis also predicted *Marinobacter* and *Roseovarius* to be dominant DMSP producing bacteria, but *Alteromonas* and *Thiobacimonas* (*Salipiger*) appeared less abundant than in the 16S rRNA amplicon analysis. The metagenomic Dsy*B* sequences were mostly homologous to *Roseobacter* clade bacteria such as *Roseovarius*, *Thalassobaculum*, *Albimonas*, and the MmtN sequences most closely aligned to *Roseovarius*, *Labrenzia*, and *Rhodobacter* MmtN. There were no detectable *TpMMT* genes within the metagenomic data. However, there were some algal *DSYB* sequences identified	Bacterial DMSP catabolic genes and their transcripts followed the same trend of being largely enhanced in transitional and seawater samples with higher DMSP levels than freshwater samples. The metagenomics analysis showed that *dddP* is significantly more abundant than *dmdA* in all tested samples. The *dddP* sequences were closely related to *dddP* genes from *Rhodobacteraceae* (e.g. *Roseovarius* and *Ruegeria*) as well as some *Alphaproteobacteria* (e.g. *Rhodobacterales*) and Fungi (e.g. *Fusarium*). The metagenomic DmdA sequences were mainly homologous to *Pelagibacter* (SAR11 clade) and *Rhodobacteraceae* (e.g. Roseobacter, Roseovarius) enzymes. The *dddQ* sequences most closely aligned to DddQ from *Rhodobacteraceae* (e.g. *Roseovarius* and *Ruegeria*) and *Pelagibacteraceae* as well as other Alphaproteobacteria (e.g. *Rhodospirillaceae*, *Rhizobiales*). The DddL	(Sun *et al*., 2021)

(Continues)

Table 1. Continued

Regions	DMSP biosynthesis	DMSP cleavage	References
		sequences were most homologous to *Rhodobacteraceae* (e.g. *Oceanicola*, *Rhodobacter*, and *Labrenzia*) and other Proteobacterial DddL enzymes, including, *Rhodospirillaceae* and *Marinobacter*. No eukaryotic *Alma1* DMSP lyase sequences were found in the metagenome data	
Monterey Bay, CA	NA	The *dmdA* genes were 1.9-fold more abundant in Monterey Bay. Genes *dddP* and *dddK* dominating the Monterey Bay DMSP cleavage gene pool were found in 9.8% and 7.2% of cells. The *dmdA* gene was harboured by members of the *Alphaproteobacterial* and the *Gammaproteobacteria*. The *dddK* gene was present in only a subset of SAR11 genomes. *dddP* gene sequences were placed in both *Alphaproteobacteria* and *Gammaproteobacteria*	Nowinski *et al*. (2019)
Sanriku Coastal Region in Japan	NA	The mesocosm study revealed that the *dmdA* subclade D was the major DMSP degradation gene in the free-living (FL) and particle-associated (PA) fractions. The *dddD* gene was found in higher abundance than the *dddP* gene in all the tested samples. SAR11 bacteria containing the *dmdA* subclade C/2 were likely the dominant DMSP consumer and G*ammaproteobacteria* containing *dddD* the dominant DMS producer in the Oyashio (OY) Current characterized by cold, low-salinity, and nutrient-rich water. On the other hand, SAR11 bacteria possessing *dmdA* subclade D were the dominant DMSP consumer and the marine Roseobacters possessing *dddP* were likely the dominant DMS producer in the Tsugaru Warm (TW) Current characterized by warm, saline, and relatively nutrient-poor water	Cui *et al*. (2020)

NA, data not available.

Table 2. DMSP production in bacterial and phytoplanktons strains.

Strains	Intracellular DMSP concentration (mM)	Conditions/ growth medium	References
Emiliania huxleyi		Temperature stress	McParland *et al*. (2020)
	145 ± 19	Control: T_{opt} (23°C)	
	323 ± 50	<T_{opt} (14°C)	
	307 ± 49	<T_{opt} (16°C)	
	198 ± 26	<T_{opt} (20°C)	
	67 ± 9	>T_{opt} (26°C)	
	119 ± 17 ns	>T_{opt} (28°C)	
		NO_3^- stress	
	165 ± 23	Control: N_{ss}^+	
	132 ± 24	N_{ss}^-	
	146 ± 36 ns	N_{ss}^{--}	
		Salinity stress	
	57 ± 10	Control: Opt salinity (35‰)	
	48 ± 6 ns	<Opt salinity (25‰)	
	50 ± 8 ns	<Opt salinity (30‰)	
	82 ± 13	>Opt salinity (40‰)	
	133 ± 28	>Opt salinity (45 or 50‰)	
Thalassiosira oceanica		Temperature stress	
	7 ± 1	Control: T_{opt} (23°C)	
	10 ± 2	<T_{opt} (14°C)	
	9 ± 1	<T_{opt} (16°C)	
	8 ± 1	<T_{opt} (20°C)	
	2 ± 0.2	>T_{opt} (26°C)	
	2 ± 0.2	>T_{opt} (28°C)	
		NO_3^- stress	
	4 ± 0.3	Control: N_{ss}^+	
	8 ± 0.3	N_{ss}^-	
	12 ± 0.5	N_{ss}^{--}	
		Salinity stress	
	0.9 ± 0.1	Control: Opt salinity (35‰)	
	-	<Opt salinity (25‰)	
	-	<Opt salinity (30‰)	
	4 ± 0.4	>Opt salinity (40‰)	
	14 ± 1	>Opt salinity (45 or 50‰)	
Labrenzia aggregata LZB033	9.6	MBM (minimal, 0.5 mM NH_4Cl)	Curson *et al*. (2017)[a]
Labrenzia aggregata IAM 12614	5.1	MBM (minimal, 0.5 mM NH_4Cl)	
Pseduooceanicola batsensis HTCC2597	6.3	YTSS (complete)	
Pelagibaca bermudensis HTCC2601	40.6	YTSS (complete)	
Sediminimonas qiaohouensis DSM21189	19.1	Marine broth 2216+ 3% NaCl (complete)	
Sagittula stellata E-37	1.7	MBM (minimal)	
Amorphus coralli DSM19760	1.3	YTSS (complete)	
Thalassobaculum salexigens DSM19539	0.8	Marine broth 2216 (complete)	
Chrysochromulina tobin CCMP291	0.611 ± 0.08	NA	Curson *et al*. (2018)
Chrysochromulina sp. PCC307	0.196 ± 0.0394		
Fragilariopsis cylindrus CCMP1102	6.71 ± 0.92		
Symbiodinium microadriaticum CCMP2467	282 ± 35.0		
Prymnesium parvum CCAP946/6	54.3 ± 5.97		
Prymnesium parvum CCAP941/6	20.6 ± 3.05		
Prymnesium parvum CCAP946/1A	53.8 ± 4.58		
Prymnesium parvum CCAP946/1D	35.5 ± 1.50		
Prymnesium parvum CCAP946/1B	48.4 ± 6.29		
Prymnesium patelliferum CCAP946/4	25.3 ± 2.39		
Alexandrium minutum	3387.6 ± 121.9	Algal cells were suspended in 20 ml of 38‰ NaCl solution and stored at −80°C until intracellular DMSP analysis	Jean *et al*. (2005)
Dinophysis acuminata	477.4 ± 64.3		
Prorocentrum arcuatum	442.2 ± 22.9		
Protoperidinium pellucidum	133.5 ± 13.5		
Ceratium furca	37.5 ± 2.1		
Prorocentrum sp. IIB_2b_1	1082	Algal cultures were grown in appropriate media under identical light conditions (10^{16} quanta. $cm^2.s^{-1}$; 14:10 light: dark cycle) and at 20°C	Keller *et al*. (1989)
Heterocapsa pygmaea GYMNO	451		
Crypthecodinium cohnii CCOHNII	377		
Scrippsiella trochoidea PERI	350		
Symbiodinium microadriaticum HIPP	345		
Thoracosphaera heimii L603	194		

(Continues)

Table 2. Continued

Strains	Intracellular DMSP concentration (mM)	Conditions/ growth medium	References
Cachonina niei CACH	193		
Prorocentrum micans M12-11	190		
Heterocapsa sp. GT23	190		
Gymnodinium sp. 94GYR	125		
Gymnodinium simplex WT8	46		
Gymnodinium nelsoni GSBL	30		
Gonyaulax spinifera W1	16		
Gambierdiscus toxicus GT200A	10		
Gonyaulax polyedra GP60e	4.01		
Dissodinium lunula L823	1.94		
Gyrodinium aureolum KT3	0.65		
Gyrodinium aureolum PLY497A	0.36		
Pyrocystis noctiluca CCMP4	0.01		
Amphidinium carterae AMPHI	377	Algal cultures were grown in 100 ml batch cultures at 20°Cwith illumination of 10^{16} quanta cm^2 s^{-1} (14:10 light: dark cycle) in appropriate growth media	(Keller, 1989)
Prorocemtrum minimum EXUV	111		
Ceratium longipes 090201	0.2		
Heterocapsa triquetra CCMP449	364	NA	(Caruana, 2010)
Scrippsiella trochoidea CCMP1599	326	grown at 15°C	
Amphidinium carterae CCMP1314	300	NA	
Alexandrium minutum CCMP113	290	NA	
Crypthecodinium cohnii CCMP316	106	5% Nitrogen medium	
	69	100% Nitrogen medium	
Polarella glacialis CCMP1138	94	NA	
Kryptoperidinium foliaceum CCMP1326	56	NA	
Lingulodinium polyedrum LP2810	23	NA	
Karlodinium veneficum CCMP415	11	NA	
Amphidinium carterae CCMP1314	326	NA	Harada (2007)
Amphidinium carterae X	288	NA	
Karenia brevis CCMP2281	18	NA	
Lingulodinium polyedrum CCMP1738	13	NA	
Amphidinium operculatum CCAP1102/6	312	All cells were grown in 500 ml glass culture flasks sealed with cotton and muslin bungs and maintained at 14°C on a 14:10 Light: Dark cycle, at a photon flux density of 70 mmol m^{-2} s^{-1} supplied by cool-white fluorescent lighting	Hatton and Wilson (2007)
Scrippsiella trochoidea CCAP1134/1	169		
Prorocentrum micans SB1	87		
Amphidinum carterae CCAP1102/1	57		
Gonyaulax spinifera LY11363	48		
Gymnodinium simplex CCAP1117/3	35		
Alexandrium tamarense CCAP1119/1	20		
Lingulodinium polyedrum CCAP1121/2	5.09		
Alexandrium tamarense CCMP115	235	Cultures were maintained in the f/2-Si medium at 15°C and 80 μmol photons m^{-2} s^{-1} (14:10-h light: dark cycle) and were transferred every 7–14 days to maintain exponential growth	Wolfe *et al*. (2002)
Alexandrium tamarense CCMP116	205		
Alexandrium tamarense CCMP1771	196		
Alexandrium fundyense CCMP1719	183		
Prorocentrum minimum CCMP1329	167 ± 4	Cultures were maintained at 22°C in 125-ml polycarbonate Erlenymer flasks	Spiese *et al*. (2009)
Amphidinium carterae CCMP1314	109 ± 15		
Scrippsiella trochoidea NIES-369	600	Strains were maintained in f/2 media under a 12 h light:12 h dark cycle at 20°C	Niki *et al*. (2000)
Heterocapsa triquetra NIES-7	300		
Pfiesteria shumwayae CCMP2089	0.00425	The dinoflagellates were cultured in an f/2 medium lacking silica and supplemented with 15 parts per thousand (p.p.t.) of artificial sea salts (Instant Ocean) at 20°C with a light ± dark cycle of 14 h light (mean light intensity of 90 ± 100 μM m^{-2} s^{-1}) and 10 h dark	Miller and Belas (2004)
Pfiesteria piscicida CCMP1830	0.00344		
Asterionellopsis glacialis PR1	0.21 ± 0.007	NA	Williams *et al*. (2019)
Gyrodinium impudicum	820 ± 150	NA	Belviso *et al*. (2000)
Pelagomonas spp.	15.4 and 31.4	The culture was maintained at 19°C under continuous low blue light (14.5 μmol quanta m^{-2} s^{-1}) provided by Daylight fluorescent tubes (Sylvania) wrapped with a 'moonlight blue' Lee filter (Panavision).	Corn *et al*. (1996)
Gymodnium nelsoni	280	NA	Dacey and Wakeham (1986)

ns, not significant; YTSS: Yeast Extract Tryptone Sea Salts Medium; NA, data not available.
[a]No added methylated sulfur compounds unless stated otherwise; 10 mM succinate was carbon source for all minimal media; 10 mM NH4Cl was nitrogen source for all media unless stated otherwise.

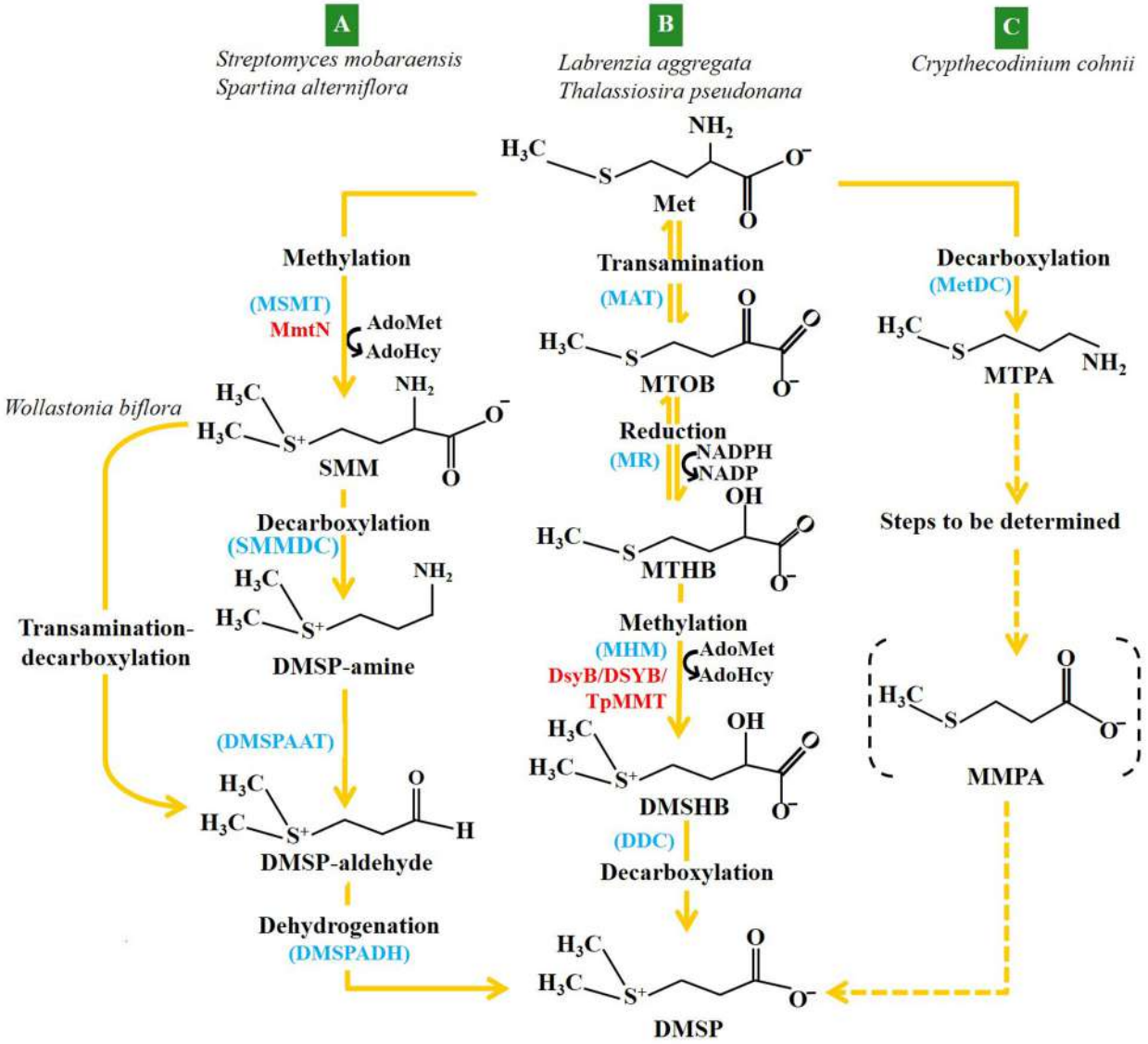

Fig. 1. DMSP biosynthesis pathways in different organisms. DMSP production in higher plants and bacteria containing *mmtN* (*Streptomyces mobaraensis*, S*partina alterniflora*, *Wollastonia biflora* (A); macroalgae (*Ulva*), diatoms (*Thalassiosira pseudonana*, *Melosira*), prymnesiophytes (*Emiliania*), prasinophytes (*Tetraselmis*) and algae that contain *DSYB* and bacteria that contain *dsyB* (B); and the dinoflagellate *Crypthecodinium cohnii* (C). The dotted line represents a suggested, but as yet unconfirmed, pathway. In *W. biflora*, SMM is converted to DMSP aldehyde via an unconfirmed process, not through DMSP-amine. In *S. alterniflora*, the conversion of DMSPamine to DMSPaldehyde is found to be O_2-dependent, implicating an oxidase instead of a transaminase as a catalyst for this step. Enzymes involved in the pathways are shown in blue and genes in red. MSMT, methionine *S*-methyltransferase; SMMDC, SMM decarboxylase; DMSPAAT, DMSPamine aminotransferase; DMSPADH, DMSP-aldehyde dehydrogenase; MAT, Met aminotransferase; MR, MTOB reductase; MHM, MTHB methyltransferase; DDC, DMSHB decarboxylase Met, methionine; SMM, *S*-methyl-methionine; MMPA, methylmercaptopropionate; MTPA, 3-methylthiopropylamine; DMSHB, 4-dimethylsulfonio-2-hydroxybutyrate.

oxidation (Curson *et al*., 2018; Liao and Seebeck, 2019). An *in silico* analysis of the *bur* gene locus revealed candidate genes for a methyltransferase (BurB), a decarboxylase (BurI), a transaminase (BurD), and a dehydrogenase (BurE) (Trottmann *et al*., 2020) (Fig. S2).

DMSP synthesis in algae. Production of DMSP is confined to a few classes of phytoplankton, primarily the *Dinophyceae* (*dinoflagellates*) and *Prymnesiophyceae* (which includes the *coccolithophores*) (Keller *et al*., 1989; Curson *et al*., 2018). In addition to these organisms, DMSP production has been reported in diatoms, the red alga *Polysiphonia*, and the green alga *Ulva intestinalis* (Challenger and Simpson, 1948; Gage *et al*., 1997; Summers *et al*., 1998; Lyon *et al*., 2011; Kettles *et al*., 2014). DMSP synthesis occurs through the

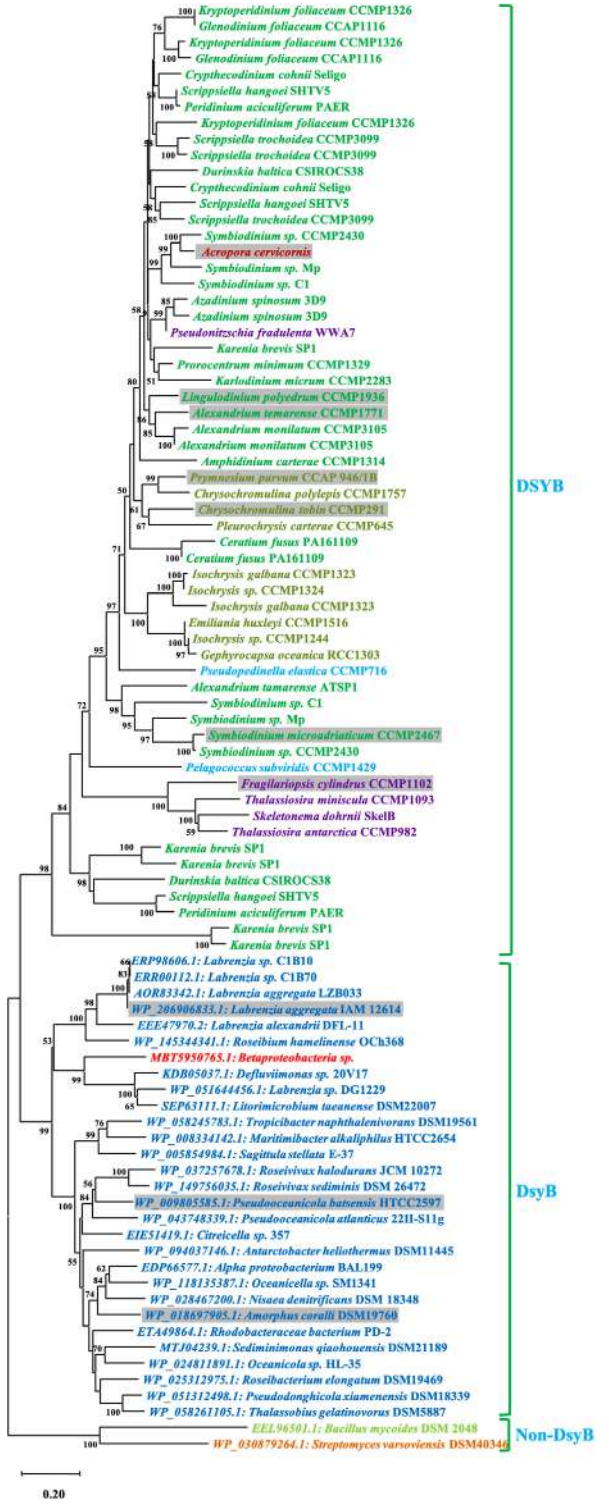

Fig. 2. Neighbour-joining phylogenetic tree of DsyB/DSYB proteins. Taxonomic groups are highlighted by different colours Bacilli-light green; Actinobacteria-orange; Betaproteobacteria-red; Alphaproteobacteria-blue; Anthozoa-dark red; Prymnesiophyceae-olive green; Dinophyceae-green; Bacillariophyceae-purple; and Dictyochophyceae-light blue. The shaded colours represent the functional proteins. Bootstrap support for nodes is indicated.

transamination and decarboxylation pathway in the algae (Fig. 1). *DSYB* gene encoding DSYB enzyme is a eukaryotic homologue of *dsyB*. It has been reported that DSYBs in the eukaryote originated from prokaryotic DsyBs early in their evolution and later were transferred to eukaryotes either through endosymbiosis during time of mitochondrial origin or more recently by horizontal gene transfer (HGT) (Curson *et al*., 2018). DSYB enzyme has been reported to be functional in diatoms such as *Fragilariopsis cylindrus* CCMP1102, dinoflagellates such as *Alexandrium tamarense* CCMP1771, *Lingulodinium polyedrum* CCMP1936, *Symbiodinium microadriaticum* CCMP2467 and prymnesiophytes such as *Chrysochromulina tobin* CCMP291 and *P. parvum* CCAP946/1B (Curson *et al*., 2018) (Fig. 2). The intracellular DMSP concentrations in these strains are given in Table 2. *Alexandrium minutum* and *Alexandrium pacificum*, and *Alexandrium fundyense* were reported to produce DMSP (Caruana and Malin, 2014; Caruana *et al*., 2020). Still, the synthesis pathway of DMSP in dinoflagellates and *Alexandrium* remains to be determined (Fig. 1). Increased *DSYB* transcription, DSYB protein levels and DMSP concentration in *P. parvum* have been observed in response to increased salinity, where might function as an significant osmolyte. In *F. cylindrus*, DMSP production and *DSYB* transcription increased with nitrogen limitation and increased salinity, but the latter might support DMSP in osmoregulation (Curson *et al*., 2018). Both *C. tobin* CCMP291 and *Chrysochromulina* sp. PCC307, the two haptophytes that adapted to different salinity levels (fresh-brackish and marine waters, respectively) did not respond to either condition. In contrast, the function of TpMMT (TpMT2) encoded by the gene *TpMT2* was only confirmed in *T. pseudonana*. The TpMT2 showed high similarity with the proteins from *Thalassiosira oceanica* (76%), *Phaeodactylum tricornutum* CCAP 1055/1 (57%), but were not shown to be functional and had low similarity of 12% with DsyB of Alphaproteobacteria. TpMT2 protein concentrations in *T. pseudonana* were found to be regulated in response to both salinity changes and nitrogen limitation (Kageyama *et al*., 2018). Among DMSP-producing phytoplankton, the intracellular DMSP concentration varies greatly among groups and within genera (Caruana and Malin, 2014) and is generally high in dinoflagellates (3.4 M) and haptophytes (413 mM) and lowest in diatoms (generally <50 mM) (Keller *et al*., 1989). The dinoflagellate *S. microadriaticum* CCMP2467 produces high DMSP concentrations (282 mM) (Caruana and Malin, 2014; Curson *et al*., 2018). Significant intra-group variation in DMSP production is seen with some representatives producing DMSP below detectable levels (Keller *et al*., 1989; Caruana and Malin, 2014). DMSP producers can be divided into two groups based on

cellular DMSP levels and changes in these levels in response to environmental stressors: high DMSP producers (HiDPs) that contain ≥50 mM intracellular DMSP and low DMSP producers (LoDPs) that contain <50 mM (McParland and Levine, 2019; McParland *et al*., 2020). It is suggested that HiDPs may not significantly alter cellular DMSP levels due to nutrient stress, whereas LoDPs seemed to respond with considerable changes in cellular DMSP (Stefels *et al*., 2007). It is hypothesized that DMSP may be expressed constitutively in HiDPs, whereas it may be regulated as a stress growth response in LoDPs (McParland and Levine, 2019). The hypothesis of differential regulation of DMSP under nutrient limitation was recently further supported with the first direct comparison of a HiDP and LoDP (McParland *et al*., 2020). Currently, it has been suggested that the eukaryotic DMSP synthesis genes such as *DSYB* and *TPMT2* may be marker genes for HiDPs and LoDPs groups, respectively. Both *DSYB* and *TPMT2* genes are globally abundant in *in situ* eukaryotic metatranscriptomes. Most known LoDPs exhibits *TpMT2* genotypes and some exhibit *TpMT2* + *DSYB* genotypes, whereas HiDPs exhibits *DSYB* genotypes (McParland *et al*., 2021).

DMSP synthesis in animals. Besides algae and bacteria, DMSP synthesis has also been reported in some species of corals such as *Acropora* (Raina *et al*., 2013). The juveniles of *Acropora millepora* and *Acropora tenuis* lacking photosynthetic symbionts, when subjected to thermal stress (32°C), showed significantly increased concentrations of DMSP levels detected through nuclear magnetic resonance (NMR) spectroscopy (Tapiolas *et al*., 2013). Such increase in the DMSP level was also seen in adult reef-building corals when subjected to thermal stress (Raina *et al*., 2013). Further, an LC–MS-based method provides accurate measurements of DMSP from nanomolar to high micromolar concentrations in corals (Li *et al*., 2010). It has been suggested that nutrient history can influence the response of scleractinian corals to thermal stress (Hadjioannou *et al*., 2019). Recently, it has been shown that natural stressors on the staghorn coral *A. intermedia* in the field, and stress from added dissolved inorganic phosphorus (DIP) and tripolyphosphate (TPP) at high seawater temperatures caused corals to bleach, whilst extracellular DMSP, intracellular and tissue DMSP concentrations increased (Fischer and Jones, 2021). DMSP, DMS and DMSO can potentially be used as antioxidant defence by corals (Deschaseaux *et al*., 2014; Jones and King, 2015). Orthologues of the eukaryotic *DSYB* gene encoding a SAM-dependent methyltransferase in the coral *Acropora cervicornis* catalyses the important step in DMSP production through the transamination pathway (Fig. 1). It has been suggested that biosynthesis of DMSP in corals occurs through HGT of *DSYB* from dinoflagellates. Nonetheless, it is possible that DSYB sequences in the coral might be contaminant sequences inadvertently isolated from their symbionts (Curson *et al*., 2018). DMSP production has been recorded in other animals such as mussels, giant clams, anemones and benthic flatworms (White *et al*., 1995; Hill *et al*., 2000; Van Alstyne *et al*., 2009). The concentration of DMSP in the coral *Acropora cytherea* and the giant clam *Tridacna maxima* varied according to the complexity of species assemblages (Guibert *et al*., 2020).

DMSP synthesis in plants. DMSP production has been reported in *Spartina* species (Kocsis *et al*., 1998), sugarcanes (Paquet *et al*., 1994), maize (Ausma *et al*., 2017) and the angiosperms *W. biflora* (Hanson *et al*., 1994). Biosynthesis of DMSP in cordgrass *Spartina anglica* was suggested to be the main source of DMSP and DMS in most saltmarshes (Yoch, 2002), but recent finding indicates that associated bacteria in the *S. anglica* rhizosphere and phyllosphere are the possible contributors (Williams *et al*., 2019). DMSP production in plants takes place through methylation pathway (Fig. 1) (Hanson and Gage, 1996; Kocsis *et al*., 1998), which commences with *S*-methylation and ends with oxidation with transamination and decarboxylation occurring either individually in *Spartina alterniflora* or as combined steps-in *Wollastonia biflora* (Kageyama *et al*., 2018).

DMSP catabolism

Marine heterotrophic bacteria import and degrade DMSP using three known metabolic pathways, that is, the demethylation, the cleavage and the oxidation pathway (Fig. 3). Recently, using the sulfur isotope determining technique in the quantitating assessment of the sulfur partitioning, it has been indicated that sulfur isotope fractionations constrain the biological cycling of DMSP in the upper ocean and it was shown that the residual DMSP from the demethylation pathway is 2.7‰ enriched in $\delta^{34}S$ relative to the initial DMSP and that the fractionation factor ($^{34}\varepsilon$) of the cleavage pathways varies between 1% and 9‰. This supports the notion that demethylation dominates over cleavage in marine environments (Osorio-Rodriguez *et al*., 2021). In this section, structure and mechanism of several enzymes involved in DMSP catabolism will be discussed.

DMSP demethylation pathway. Here, we have focused on recent work on several Dmd enzyme (Schuller *et al*., 2012; Tan *et al*., 2013; Shao *et al*., 2019; Wirth *et al*., 2020).The enormous amounts of DMSP believed to be catabolized by marine bacteria through the demethylation pathway involves a series of 'Dmd' enzymes

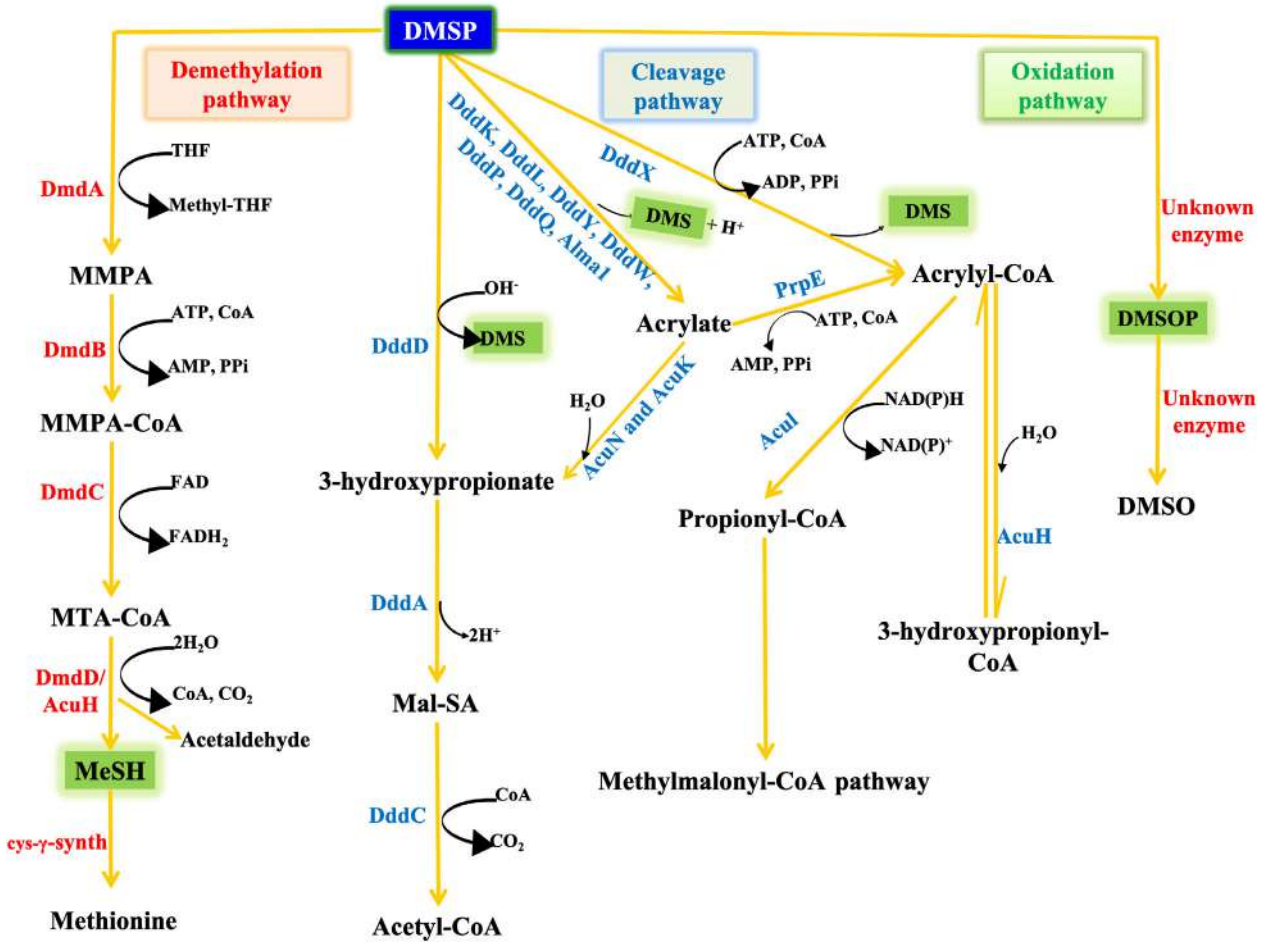

Fig. 3. Biochemical pathways for dimethylsulphoniopropionate catabolism. In the cleavage pathways, several DMSP lyases DddL, DddP, DddQ, DddW, DddK, DddX, DddY or algal Alma1 catabolizes DMSP to acrylate with the release of dimethyl sulfide (DMS), and acrylate is then converted to 3-hydroxypropionate (3HP) by the action of AcuN and AcuK, whereas the DMSP lyase DddD converts DMSP to 3HP. 3HP is then converted to malonate semi-aldehyde (Mal-SA) and then acetyl-CoA by DddA and DddC, respectively. An acrylate-CoA ligase (PrpE), an acryloyl-CoA reductase (AcuI) and AcuH are also involved in the cleavage pathway. The DMSP demethylation pathway is catalysed by the DMSP demethylase (DmdA), MMPA-CoA ligase (DmdB), MMPA-CoA dehydrogenase (DmdC), and either the MTA-CoA hydratase (DmdD) or acrylate utilization hydratase (AcuH). In the oxidation pathway, DMSP is oxidized to dimethylsulfoxonium propionate (DMSOP). However, enzyme involved in this pathway is unknown.

namely DmdA, DmdB, DmdC and DmdD/AcuH. These Dmd enzymes collectively catabolize DMSP to acetaldehyde and MeSH for use as carbon and sulfur sources, respectively. In the first step, DmdA enzyme catalyses a redox-neutral methyl transfer reaction from DMSP to tetrahydrofolate (THF) and produces 3-methylmercaptopropionate (MMPA) and 5-methyl-THF (Howard *et al*., 2006; Schuller *et al*., 2012). Furthermore, MMPA is degraded by the ligation of CoA through MMPA CoA ligase DmdB to produce MMPA-CoA, which is then dehydrogenated by the MMPA-CoA dehydrogenase DmdC to yield methylthioacryloyl-CoA (MTA-CoA). Finally, the MTA-CoA hydratase DmdD catalyses the hydration and hydrolysis of MTA-CoA. As a result, acetaldehyde and MeSH are formed (Reisch *et al*., 2011b). The metabolism of reduced sulfur compounds in the marine Roseobacters is complex, as some organisms producing MeSH from MMPA despite the lack of *dmdA* gene in their genome (González *et al*., 1999). These organisms possess DmdBCD/acuH and degrade MMPA to produce MeSH instead of DMSP catabolism. MeSH can then be assimilated into biomass or broken down to formaldehyde and H_2S. In addition, only 33% and 50% of the methionine is recently reported to be biosynthesized from the MeSH in *R. pomeroyi* and *R. lacuscaerulensis*, respectively ('direct capture' pathway). The remaining methionine was biosynthesized by the random assembly of free sulfide and methyl-THF derived from DMSP ('reassembly' pathway) (Wirth *et al*., 2020). Using an isotopic labelling strategy to track DMSP sulfur and carbon assimilations, it has been demonstrated that the direct capture of methanethiol is not

the primary pathway used for methionine biosynthesis in two *Ruegeria* species (Wirth *et al*., 2020).

DMSP demethylase A (DmdA). dmdA gene encoding DmdA enzyme was first reported in the Roseobacter group bacterium *Ruegeria pomeroyi* DSS-3 (Howard *et al*., 2006). DmdA is a member of aminoethyltransferase/glycine cleavage T protein (AMT/GCV_T) family and use THF as the cofactor (Hernández *et al*., 2020). Especially, the residues that cooperate with the folate moiety and those participated in the ring stacking of THF are reported to be highly conserved (Lee *et al*., 2004; Reisch *et al*., 2008; Schuller *et al*., 2012). DmdA orthologues present in most of the sequenced members of the Rhodobacteraceae family, as well as bacterioplankton strains of SAR11, SAR324, SAR116 and in marine Gammaproteobacteria (González *et al*., 1999; Gonzalez *et al*., 2003; Howard *et al*., 2006; Bürgmann *et al*., 2007; Reisch *et al*., 2008) like Chromatiales, which could have acquired *dmdA* gene by HGT (Howard *et al*., 2006; González *et al*., 2019). This phylogenetic distribution suggested an expansion of *dmdA* through HGT events between different lineages of bacteria, presumably through viruses (Raina *et al*., 2010). Homologues of the *dmdA* gene are reported in 58% of cells sampled in the GOS metagenome and in at least 80% of Roseobacter cells and 40% of SAR11 cells sampled in the Sargasso Sea metagenome. *dmdA* genes are grouped into 5 clades and 14 subclades based on their nucleotide and amino acid sequences (Howard *et al*., 2006; Howard *et al*., 2008; Varaljay *et al*., 2010). *dmdA* gene appears to be part of a conserved operon, its evolution might be linked to genes such as *dmdB*, *dmdC*, and *dmdD* (González *et al*., 2019). Recently, both *dmdA* and phage-like gene transfer agent (GTA) capsid protein gene (g5) sequence has been reported in Antarctic strain *Roseicitreum antarcticum* ZS2–28, which support the hypothesis of HGT for *dmdA* among taxonomically heterogeneous bacterioplankton, and suggest a wide distribution of functional gene (i.e. *dmdA*) in global marine environments (Zeng, 2019). Currently, it has been reported that DmdA is a new gene family originated from GCV_T genes by duplication and functional divergence driven by positive selection before a coevolution between Roseobacter and phytoplankton (Hernández *et al*., 2020). It was suggested that Roseobacter acquired *dmdA* by HGT prior to an environment with higher DMSP (Hernández *et al*., 2020). It was proposed that the ancestor of the pathway that carried the DMSP demethylation pathway genes evolved in the Archean and was exposed to a higher concentration of DMSP in a sulfur-rich atmosphere and anoxic ocean, compared to recent Roseobacter eco-orthologues (*Candidatus* Puniceispirilum marinum IMCC1322, ADE38317.1 and the Roseobacter clade), which should be adapted to lower concentrations of DMSP (Hernández *et al*., 2020). The structure of the apoenzyme DmdA has been reported from *Pelagibacter ubique*, which is a tridomain structure similar to the GCV_T (Dey, 2017). In DmdA, domain 1 (residues 1–62 and 150–248) possesses a single Greek Key motif enclosed by three alpha helices, domain 2 (residues 63–149 and 249–288) is made up of a five-stranded antiparallel beta sheet with alpha helices on either side and the C-terminal domain 3 (residues 289–369) is reported to form a distorted jelly roll. DmdA enzyme active site is situated in a cleft between domains 1 and 2 (Schuller *et al*., 2012). DmdA enzyme is reported to catalyse the redox-neutral methyl transfer reaction from the substrate DMSP, which is undoubtedly distinct from GCV_T proteins, dimethylglycine oxidase and sarcosine oxidase (Schubert *et al*., 2003; Dey, 2017). The tyrosine residue (Y206) is a conserved feature of the THF-binding motif in DmdA and gives a hydrogen bond to the amine group of the folate ring on the C-2 carbon atom. In addition, acidic residues, such as E63, D108 and E204, are found within hydrogen bonding range of THF or H_2O molecules. The hydrogen bonding interaction between THF N-8 nitrogen and the protein backbone carbonyl of serine residue (S122) is consistent with a mechanism for making the N-5 nitrogen atom a better nucleophile to attack the methyl group on the sulfonium atom of substrate DMSP. The products of methyl transfer reaction are N5-methyl-THF and MMPA (Schuller *et al*., 2012).

3-Methylmercaptopropionyl-CoA ligase DmdB. The enzyme MMPA-CoA ligase DmdB catalyses the production of MMPA-CoA and is more widely distributed than DmdA (Bullock *et al*., 2017). In *R. pomeroyi* DSS-3, two forms of DmdB, RPO_DmdB1 and RPO_DmdB2, exist, whereas in the ubiquitous SAR11 clade bacterium '*Candidatus* Pelagibacter ubique' HTCC1062, only a single form of this enzyme, designated PU_DmdB1, is reported (Reisch *et al*., 2011b). Recently, the crystal structure of DmdB protein from *Ruegeria lacuscaerulensis* ITI_1157 (WP_005982887.1) has been characterized. DmdB functions as a dimer and each monomer is composed of a large N-terminal domain (Met1 to Arg432, the N domain) and a small C-terminal domain (Ser433 to Gly539, the C-domain). The N domain is made up of three beta sheets (sheets 1, 2 and 3) and six helices, which are sandwiched between sheets 1 and 2, whereas the C-domain forms a three-stranded beta sheet (sheet 4) with three helices on its face (Shao *et al*., 2019). The catalytic mechanism of DmdB has been proposed in Roseobacters. The lysine residue (Lys523) in DmdB plays an important role in catalysis and is conserved in both marine and terrestrial bacteria. DmdB undergoes two conformational changes during catalysis. At first, the binding of an ATP molecule leads to a conformational change in DmdB from the open conformation to the

adenylate-forming conformation after a 64° rotation of the C-domain. MMPA is maintained by amino acid residues His231, Trp235 and Gly302 when it enters the active site and acts as the nucleophilic base to attack the Pα of ATP, which weakens the Pα—O bond of ATP. The production of the Pα—O bond between the α-phosphate and the carboxyl oxygen of MMPA causes the splitting of the Pα—O bond between the α-phosphate and the β-phosphate. After this, the intermediate MMPA-AMP is formed, which is then ready to accept the coenzyme. Second, after a 140° rotation of the C-domain, DmdB forms the thioester-forming conformation. The CoA is maintained by multiple amino acids residues, namely Asp435, Lys438, Gly440, Gly441, Glu442, Trp443 and Glu474. The sulfhydryl sulfur of CoA attacks the carbonyl carbon of MMPA-AMP, which weakens the C—O bond, followed by the production of the C—S bond between MMPA and CoA resulting splitting of the C—O bond between MMPA and AMP and the S—H bond of CoA. Then, CoA replaces AMP and, the MMPA-CoA is produced. The proposed catalytic cycle is adopted by most of the bacterial DmdBs (Shao *et al*., 2019).

MMPA-CoA dehydrogenase DmdC. The SPO3804 gene, immediately upstream in the *R. pomeroyi* DSS-3 genome, was annotated as acyl-CoA dehydrogenase and encodes DmdC enzyme catalyzing the production of MTA-CoA. To date, three DmdC isozymes in the DSS-3 genome have been identified and shown to have activity towards MMPA-CoA (Reisch *et al*., 2011b). The crystal structure of DmdC protein (WP_009812433.1) from *Roseovarius nubinhibens* ISM reveals that it is a homodimer and each DmdC monomer is composed of four functional domains: an N-terminal α-helical domain (α-domain 1, residues 1–64 and 73–155), a 10-stranded β-sheet domain (residues 65–72 and 156–280), a central α-helical domain (α-domain 2, residues 281–452) and a C-terminal α-helical domain (α-domain 3, residues 453–593) (Shao *et al*., 2019). According to earlier work on acyl-CoA dehydrogenases (Massey and Ghisla, 1974; Pohl *et al*., 1986; Kim *et al*., 1993; Thorpe and Kim, 1995; Tamaoki *et al*., 1999; Gulick *et al*., 2004), the catalytic mechanism of DmdC for MMPA-CoA redox reaction was proposed in Roseobacters. The Phe195 and Glu435 are key residues for DmdC activity and are responsible for flavin adenine dinucleotide (FAD)-binding and MMPA-CoA catalysis, respectively. It has been reported that the FAD is stabilized by several residues, namely Met161, Thr170, Phe195, Ser197 and Tyr434, in the active centre of DmdC, whereas the fatty acyl portion of MMPA-CoA is sandwiched between Glu435 and FAD. The negatively charged carboxyl group of Glu435 acts as the nucleophilic base in order to attack the Cα hydrogen of MMPA-CoA, and the abstraction of the proton from the Cα causes the production of a Cα carbanion. The carbanion then attacks Cβ, which weakens the Cβ—H bond of MMPA-CoA, and the Cβ hydrogen, as a hydride ion, is directly transferred to the N5 position of FAD causing the formation of Cα═Cβ of MTA-CoA. When FAD takes up the hydride, the carbonyl oxygen adjacent to the N1 becomes negatively charged. As a result, MMPA-CoA is then dehydrogenated by DmdC to produce MTA-CoA. The proposed catalytic cycle is universally present in most of the bacterial DmdCs (Shao *et al*., 2019).

MTA-CoA hydratase DmdD. DmdD enzyme catalyzing the release of MeSH was identified in *R. pomeroyi* DSS-3 as enoyl CoA hydratase (SPO3805), which belongs to crotonase superfamily (cd06558). It is not widely distributed and is absent in the most of marine bacteria which use the demethylation pathway, i.e., contain DmdA enzyme. An orthologue of DmdD, named AcuH for acrylate utilization hydratase, was reported in DmdD negative strains of *R. lacuscaerulensis* and in *R. pomeroyi* (Reisch *et al*., 2011b). The crystal structure of wild-type *R. pomeroyi* DmdD free enzyme has been determined. DmdD is a hexamer and consists of a dimer of trimers where the three monomers of each trimer are related by a crystallographic threefold axis. DmdD monomer has two domains, namely the N-terminal domain (NTD) and the C-terminal domain (CTD). The NTD adopts the typical spiral crotonase fold (β-β-α superhelix, β1–β11 and α1–α8), which is organized around two roughly perpendicular β-sheets. The CTD is composed of three α-helices (α9–α11) followed by a long loop at the extreme C terminus of the protein and mediates the hexamerization of DmdD. The long loop at the C terminus is also involved in the formation of the CoA-binding site of a neighbouring monomer of the hexamer (Tan *et al*., 2013). DmdD is reported to catalyze the efficient hydration and hydrolysis of MTA-CoA, which is analogous to the canonical crotonase enzymes, and likely uses a similar mechanism, with Glu121 as the general base and Glu141 as the general acid. In DmdD, the Glu141 residue either directly attacks the carbonyl carbon of the CoA ester through an anhydride mechanism or activates a water molecule to catalyze CoA ester hydrolysis. MTA-CoA is converted to malonyl semi-aldehyde by DmdD with hydration followed by MeSH release and hydrolysis to eliminate CoA. This compound can spontaneously decompose, producing CO_2 and acetaldehyde (Tan *et al*., 2013).

DMSP cleavage pathways. Here, we have concentrated on most recent findings (Alcolombri *et al*., 2014; Hehemann *et al*., 2014; Li *et al*., 2014; Alcolombri *et al*., 2015; Brummett *et al*., 2015; Wang *et al*., 2015; Brummett and Dey, 2016; Sun *et al*., 2016; Li *et al*., 2017; Schnicker *et al*., 2017; Peng *et al*., 2019; Li *et al*., 2021).

The DMSP lyase pathway functions in several organisms such as bacteria, eukaryotic phytoplankton, macroalgae and fungi and produces DMS and acrylate or 3-hydroxypropionate (Kiene and Bates, 1990; Curson *et al*., 2011a; Brummett *et al*., 2015). Most DMSP lyases, such as DddK, DddL, DddQ, DddY and DddW, in bacteria have been referred as cupin DMSP lyases that share common sequence motifs, together with the conserved histidine motifs (Todd *et al*., 2011; Brummett *et al*., 2015; Li *et al*., 2017; Schnicker *et al*., 2017; Lei *et al*., 2018). The cupin Ddd + enzymes also share a β-barrel-fold structure comprising eight antiparallel β-strands. The cupin superfamily proteins contain a metal ion in their active sites (Dunwell, 1998; Dunwell *et al*., 2004). In fact, all cupin-containing DMSP lyases are reported to require metal cofactors for their activity (Li *et al*., 2014; Brummett *et al*., 2015; Schnicker *et al*., 2017). DddL and DddY are bona fide DMSP lyases in the cupin superfamily. However, DddQ appears to show DMSP lyase activity as a promiscuous, side activity that stems from the shared active site architecture. The overlapping substrate and/or reaction patterns of members of this newly identified superfamily are termed the Cupin-DLL (Cupin DMSP lyase and lyase-like) superfamily (Lei *et al*., 2018).

DMSP lyase DddP. DddP enzyme (∼110 kDa), encoded by *dddP* gene, is a member of the metallopeptidase (M24 peptidase) family (Todd *et al*., 2009; Kirkwood *et al*., 2010a). Generally, an M24 peptidase hydrolyzes C—N bonds, but DddP cleaves C—S bonds (Todd *et al*., 2009; Wang *et al*., 2015). *dddP* gene is widely found in several marine bacteria, dominantly found in Roseobacters (Hehemann *et al*., 2014) and has undergone substantial HGT, as close homologues occur in more distantly related bacteria such as the Gammaproteobacterium *Oceanimonas doudoroffii* (Curson *et al*., 2012), and Alphaproteobacterium 'Candidatus Puniceis*pirillum marinum*' *IMCC1322* (the *SAR116 clade*) (Choi *et al*., 2015). In the deep ocean, the *Thioglobus*/SUP05 group members carry genes for DMSP cleavage and marine Actinomycetes species possess the genes for DMSP cleavage (Liu *et al*., 2018; Landa *et al*., 2019). Moreover, *dddP* also present in many ascomycete fungi such as *Aspergillus* spp. and *Fusarium* spp. (Todd *et al*., 2009; Kirkwood *et al*., 2010b). Among the identified bacterial DMSP lyase genes, *dddP* and *dddQ* are widely present in marine metagenomes (Curson *et al*., 2018). The crystal structures of DddP were solved from *Rl*DddP (Wang *et al*., 2015), and its topological structure was similar to that of *Rd*DddP from *Roseobacter denitrificans* Och 114 (Hehemann *et al*., 2014). *Rl*DddP is a dimer and each monomer has a two-domain: an N-terminal domain (N-domain) and a C-terminal domain (C-domain). *Rl*DddP monomer adopts a typical 'pitta-bread' fold structure and possesses 15 β-strands and 16 α-helices. Inductively coupled plasma mass spectrometry (ICP-MS) analysis suggested that *Rl*DddP contained two Fe ions (Wang *et al*., 2015). There are two Fe ions present at the active site of *Rd*DddP, but it may also contain Ni, Zn or Cu in place of Fe ions (Hehemann *et al*., 2014). A mechanism for DMSP cleavage catalyzed by *Rl*DddP has been proposed. In the absence of substrate DMSP, Asp (295, 297, 307), His371, Glu (406, 421) and a water molecule in the active site are reported to form 11 coordination bonds with the two-iron core, and Glu421 bridges Fe1 and Fe2. When the substrate DMSP access the active site of the enzyme, the movable Fe1 binds to the carboxyl group of substrate via electrostatic interaction and stabilizes the molecule in the active site, whereas Trp95, Tyr117 and Tyr366 bind to the sulfur in DMSP. This binding triggers the Cα hydrogen of substrate DMSP and the carboxyl side chain of Asp377 and weakens the interaction between Fe1 and Glu421. Asp377 acts as a nucleophilic base to attack the Cα of DMSP, causing the production of an unstable DMSP-DddP intermediate. With the production of the O—H bond of Asp377 in *Rl*DddP, the α-H of DMSP is released and the C—S bond of substrate DMSP is polarized and rapidly cleaved and then the Cα═Cβ double bond of acrylate is formed. Eventually, acrylate and DMS are generated (Hehemann *et al*., 2014; Wang *et al*., 2015).

DMSP lyase DddQ. DddQ lyase enzyme, encoded by *dddQ* gene, is a member of the cupin superfamily and exclusively occurs in Roseobacters, including *R. nubinhibens* ISM, *R. pomeroyi* DSS-3 and their close relatives (Todd *et al*., 2011). The crystal structures of DddQ from *R. lacuscaerulensis* ITI_1157 indicated that two molecules of DddQ were organized as a dimer. Each molecule contains five α-helices and eight β-sheets. DddQ is probably a zinc metalloenzyme accommodating ∼42% of Zn^{2+} ions in the active site as revealed by atomic absorption spectroscopy (AAS) (Li *et al*., 2014). Its activity is inhibited in the presence of excess Zn^{2+} owing to the binding of a second Zn^{2+} in the active site and activated by Mn^{2+} and Co^{2+} (Holmquist and Vallee, 1974; Larsen and Auld, 1989; Holland *et al*., 1995; Gomez-Ortiz *et al*., 1997; Li *et al*., 2014). Recent metal content analysis showed that in the isolated form DddQ consistently possessed ∼50% of bound iron, whereas slight amount of zinc (<1%) was reported (Brummett and Dey, 2016). It has been proposed that in the absence of the substrate DMSP, the residues His125, His129, His163 and Tyr131 in the active site coordinate Zn^{2+} to maintain the architecture of DddQ, whereas in the presence of DMSP, DddQ remains in the open form and permits the substrate DMSP to enter the active site. The

oxygen atom of the carboxyl group from DMSP forms a coordination bond with Zn^{2+} and replaces Tyr131 resulting in a 25° deviation in the residue Tyr131. Next, tyrosine residue shifts closer to the DMSP molecule. This shift permits the negatively charged oxygen atom of Tyr131 to interact with Cα proton of DMSP, causing the production of a Cα carbanion. The carbonion then attacks the Cβ, which weakens the S—Cβ bond of DMSP. This reaction cascade forms a DMSP-DddQ intermediate, in which the proton of Cα-H is abstracted, causing the splitting of the S—Cβ bond and production of Cα═Cβ double bond of DMSP, while an O—H bond of Tyr 131 in DddQ is produced. As a result, DMSP is converted to DMS and acrylate (Li *et al*., 2014). Recently, it has been reported that the residue Tyr 131 plays a relatively minor role (Lei *et al*., 2018). Another mechanism of DMSP cleavage by DddQ enzyme was proposed. In the absence of substrate DMSP, Fe(III)-DddQ is in an open conformation with Tyr131 swung away from the metal centre, which mimics the resting state of the enzyme. Upon the addition of substrate, a DMSP molecule is coordinated in a monodentate fashion via its C1 carboxylate oxygen. Tyr131 swings in to coordinate iron and three residues, His123, Tyr131 and Tyr 120, aid in attaching DMSP through cooperation with the second carboxylate oxygen, thus leading it into a proper site ready for catalysis. The appropriate placing of substrate permits Tyr120 to be in close association with the hydrogen on the C2 carbon, allowing its consequent elimination and formation of acrylate (Brummett and Dey, 2016).

DMSP lyase DddY. dddY gene, which encodes DddY enzyme, is reported in the Betaproteobacterium *Alcaligenes faecalis* strain M3A, Gammaproteobacteria, Deltaproteobacteria and Epsilonproteobacteria (Curson *et al*., 2011b). DddY (∼46 kDa) is a bonafide DMSP lyase (Lei *et al*., 2018). It is the only DMSP lyase present in the periplasm, whereas all other DMSP lyases are found in the cytoplasm (Curson *et al*., 2011b). The crystal structure of DddY was determined from the Gammaproteobacterium *A. bereziniae*. DddY contains an N-terminal domain (Ala22-Val190), which is mainly composed of α-helices and a C-terminal domain (Ser191-Pro401) that adopts a typical β-barrel fold with two conserved cupin motifs (Li *et al*., 2017). It is reported that in the absence of DMSP, residues His265, Glu269, His338 and a water molecule coordinate Zn^{2+} in the active site of DddY. When DMSP enters the active site, it displaces the water molecule and then there is a formation of a new coordination bond with Zn^{2+}. After that, the residue Tyr271 attracts the Cα—H proton of DMSP and forms a Cα carbanion, which later attacks the Cβ of DMSP, causing the breakdown of the Cβ—S bond. Eventually, DMS and acrylate are generated from the active site. Further, this suggested mechanism is prevailing in DddY proteins from Beta-, Gamma-, Delta- and Epsilonproteobacteria. Most of the residues participating in the formation of acidic zone in the cavity for substrate access, namely Tyr225, Glu227 and Glu248, coordinating Zn^{2+} such as His265, Glu269 and His338, binding DMSP such as Phe207, Tyr225, His263, Tyr271, Trp359 and Arg361 and participating in the catalysis reaction, namely Tyr223 and Tyr271, have been found to be highly conserved. However, the residue Phe207, forming the hydrophobic box which accommodates the tertiary sulfonium group of DMSP, is reported to show a comparatively low conservation, but its corresponding residues in various species exhibit similar properties (Li *et al*., 2017).

DMSP lyase DddK. DddK lyase, encoded by *dddK*, was first reported in *P. ubique* HTCC1062 and cleaves DMSP into DMS and acrylate. DMSP lyase DddK is found in SAR11 bacteria, which comprises 30% of the ocean's surface microbial community, and *dddK* transcripts are relatively abundant in marine environments. Comparisons of Pelagibacterales genomes across the Group Ia subclade show that *dddK* homologues are present in 8 of 12 Pelagibacterales Ia genomes (Sun *et al*., 2016). The crystal structures of DMSP lyase DddK from *P. ubique* HTCC1062 was determined, and it exists as a dimer in the solution (Schnicker *et al*., 2017; Peng *et al*., 2019). DddK is made up of mainly beta strands that adopt a beta-barrel fold typical of cupin superfamily members, such as DddQ and DddY (Li *et al*., 2014; Li *et al*., 2017). Recently, the catalytic mechanism of DddK from the strain *P. ubique* HTCC1062 has been proposed. The Tyr64 residue is the major catalytic residue, whereas Tyr122 is reported to promote DddK lyase activity when Tyr64 is mutated to phenylalanine residue (Peng *et al*., 2019). This is consistent with the results of a previous study (Schnicker *et al*., 2017). It has been reported that an activated water molecule possibly permits Tyr64 to be deprotonated and achieve capability to act as a catalytic base, which contradicts a previous study that suggests it is the conformational change of Tyr64 that performs this (Schnicker *et al*., 2017). In the absence of substrate DMSP, residues His56, His58, Glu62, His96 and a water molecule coordinate Mn^{2+} in the active site of DddK. When DMSP arrives at the active site of DddK, it displaces the water molecule and there is a formation of a new coordination bond with Mn^{2+}. Later, Tyr64 attacks the Cα—H proton of DMSP, causing the production of a Cα carbanion, which attacks the Cβ of DMSP, splitting the Cβ—S bond of DMSP. As a result, DMS and acrylate are liberated from the active site of DddK. The suggested mechanism for DddK is common in SAR11 bacteria with DddK (Peng *et al*., 2019).

DMSP lyase DddD. dddD gene encoding DddD enzyme was first identified in *Marinomonas* MWYL1 isolated from the rhizosphere of the saltmarsh grass *Spartina anglica* (Todd *et al*., 2007). Among different DMSP lyases, DddD forms 3-hydroxypropionate (3HP) instead of acrylate along with DMS (Todd *et al*., 2007; Todd *et al*., 2010). Most frequently, *dddD* gene is found in Gammaproteobacteria, especially in *Oceanospirillales* and *Pseudomonadales*, isolated from DMSP-rich ecosystems, such as corals, marine seaweeds and saltmarsh sediments (Ansede *et al*., 2001; Raina *et al*., 2009; Curson *et al*., 2010; Todd *et al*., 2010; Raina *et al*., 2016), and also in some other Proteobacteria, such as *Rhizobiales*, *Rhodobacterales* and *Burkholderiales* (Todd *et al*., 2007). *Endozoicomonas* species have been reported to dominate the microbiomes of diversified marine hosts existing in shallow depths or intertidal zones, such as corals in tropical and temperate reefs (Neave *et al*., 2017; van de Water *et al*., 2017). Interestingly, genomes of *Endozoicomonas* species, including *E. acroporae*, harbour a high percentage of oxidative stress-responsive genes, which provide clues for their potential to alleviate oxidative stress in the coral species. In addition, *E. acroporae*, which is usually found in varied coral genera in the Indo-pacific region, can metabolize DMSP to DMS via the DddD cleavage pathway and plays a role in the coral sulfur cycle (Tandon *et al*., 2020). Interestingly, this bacterium may also defend its host from the coral pathogen *Vibrio coralliilyticus*, which utilizes DMSP as a cue to find physiologically stressed corals (Garren *et al*., 2014). In *Marinomonas* MWYL1, *dddD* is transcribed divergently from a four-gene operon, *dddTBCR*. Such gene arrangement also occurs in *Marinomonas* MED121 and in *Marinobacter*. Both *Sagittula stellata* and *Rhizobium* NGR234 control their *dddD* genes expression through DddZ regulatory protein in place of DddR, which is used by *Marinomonas* and *Burkholderia cepacia* AMMD. Both *S. stellata* and *Marinomonas* transport the DMSP via a BCCT-type transporter (Johnston *et al*., 2008). Recently, a DddD-Rh enzyme encoded by *dddD-Rh* gene found on the plasmid Actinobacteria *Rhodococcus* sp. NJ-530 has been identified and it is very distant from the known DMSP lyase DddD in sequence and evolution (Wang *et al*., 2020). The crystal structure of DMSP lyase DddD has not been resolved yet, and the structural homology using Swiss-Model (Arnold *et al*., 2006) identified DddD's active site residues. According to this, the anticipated topology of DddD lyase enzyme is made up of two CaiB-like intertwined domains joined through a long polypeptide linker. This model also suggested that the C-domain contains the catalytic aspartate that performs CoA transfer in all class III CoA-transferases, whereas the N domain contains a short insertion (LGSSY, residues 165–169) (Alcolombri *et al*., 2014; Wang *et al*., 2020). A catalytic cycle has been purposed, in which DMSP and acetyl CoA react via an acetylated enzyme intermediate to form a DMSP covalent intermediate complex (DMSP–Enzyme CoASH), which can be employed in two alternative ways. In 'Alternative A', the DMSP enzyme intermediate is directly hydrated. Subsequently, CoA attacks to release the 3HP-CoA product. According to this model, both the transferase and lyase occur within the Asp602 site. In 'Alternative B', DMSP-CoA is generated first and then hydrated (Alcolombri *et al*., 2014). The mechanism of DMSP cleavage by DddD is still unclear.

DMSP lyase DddL. dddL gene specifies a product DddL with no close similarity to any polypeptide or domain with known function and is mainly found in the Rhodobacteraceae family of Alphaproteobacteria (Curson *et al*., 2008). DddL is a true cupin DMSP lyase, and its specific activity (70 units) is upto 10-fold higher than DddK and DddW and is well above 1000-fold higher than that of DddQ (Lei *et al*., 2018). Structural studies on DMSP lyase DddL have not yet been reported.

DMSP lyase DddW. DMSP lyase DddW, encoded by *dddW* gene, cleaves DMSP into acrylate and DMS. SPO0454 gene encoding a lysR-type transcriptional regulator, is reported to regulate *dddW* (Rinta-Kanto *et al*., 2011; Todd *et al*., 2012). In addition, SPO0454 is reported to be auto-regulatory (Maddocks and Oyston, 2008). DMSP lyase DddW is uncommon among the deduced proteomes of Roseobacters and other marine bacteria (Newton *et al*., 2010), and there are no very close DddW homologues in marine metagenomic sequences, most notably those in the GOS (Rusch *et al*., 2007). DddW is a dimeric protein, and its secondary structure is determined by circular dichroism, which is primarily a β-sheet as seen in cupin superfamily proteins such as DMSP lyase DddQ (Dunwell *et al*., 2001; Li *et al*., 2014). It accommodates various metal ions, but it favours iron binding preferentially. Stoichiometry work suggested that DMSP lyase DddW needs one Fe(II) per monomer. The residues, namely H81, H83, E87 and H121, are present within the cupin domain of DddW that is anticipated to form the metal-binding active site. The mechanism of DddW-catalyzed reaction for DMSP cleavage has been proposed. According to this, DddW recognizes Fe(II) cofactor to which the substrate DMSP can coordinates in either monodentate or bidentate fashions. His81 acts as a nucleophile to eliminate a hydrogen atom from the α-carbon of DMSP to generate acrylate. A hypothetical water molecule can be triggered by His81, which then acts as a nucleophile in starting catalysis. Tyr89 situated near the active site commences the elimination reaction cleaving DMSP (Brummett *et al*., 2015).

DMSP lyase DddX. The DMSP lyase DddX has recently been identified in *Psychrobacter sp*. D2 isolated from Antarctic samples and is an ATP-dependent DMSP lyase that can catalyse DMSP degradation to DMS and acryloyl-CoA. It belongs to the acyl-CoA synthetase (ACD) superfamily and is found in several Alphaproteobacteria (*Pelagicola sp*. LXJ1103), Gammaproteobacteria (*Psychrobacter sp*. P11G5; *Marinobacterium jannaschii*), and Firmicutes (*Sporosarcina sp*. P33). The crystal structure of DddX in complex with ATP has been solved. There are four DddX monomers arranged as a tetramer in an asymmetric unit. Each DddX monomer possesses a CoA-binding domain and an ATP-grasp domain. The molecular mechanism of DddX catalysis on DMSP has been proposed. Firstly, His292 is phosphorylated by ATP, forming phosphohistidine. Next, the phosphoryl group is transferred from phosphohistidine to the DMSP molecule to generate DMSP-phosphate, which is subsequently attacked by CoA to form DMSP-CoA Intermediate. Then, residue Glu432 acts as a general base to attack DMSP-CoA. Finally, acryloyl-CoA and DMS are generated and released from the catalytic pocket of DddX (Li *et al*., 2021).

DMSP lyase Alma1. Alma1 gene, which encodes Alma1 enzyme, was identified and characterized from bloom-forming algae *Emiliania huxleyi* (*Ehux*) (Alcolombri *et al*., 2015). Alma1 lyase is a homotetramer, belongs to the Asp/Glu/hydantoin racemase superfamily (Glavas and Tanner, 2001) and forms DMS and acrylate from DMSP like most bacterial DMSP lyases. It is evolutionary and mechanistically different from previously identified marine bacterial DMSP lyases (Reisch *et al*., 2011; Moran *et al*., 2012). The racemase superfamily catalyses the abstraction and/or addition of a proton from a carbon next to a carboxylate. According to this, Alma1 lyase catalyses proton abstraction at the same site leading to β-elimination. Finally, DMS and acrylate are released (Alcolombri *et al*., 2015). Based on protein sequence similarity, orthologues of Alma1 and its paralogues from *E. huxleyi* are found in a broad range of eukaryotes, including haptophyte, dinoflagellates, corals and some bacteria (Yost and Mitchelmore, 2009; Alcolombri *et al*., 2015). Recently, it has been reported that Alma1 is the most duplicated gene in *Acropora* coral ancestor (Shinzato *et al*., 2021). There are seven Alma1 paralogues within the *E. huxleyi* genome, and four clades (A, B, C and D) of *Alma* paralogues have been reported (Alcolombri *et al*., 2015). Recently, DMSP lyase *Sym*-Alma from a coral symbiont, the dinoflagellate *Symbiodinum*-A1 (*Sym*), was reported, and it shows 45% amino acid similarity to *Ehux*-Alma1. The *Ehux*-Alma1 is not inhibited by ethylene diamine tetra acetic acid (EDTA), whereas *Sym*-Alma is inhibited by it and regains its activity in the presence of Ca^{2+} or Mn^{2+} ions but not with Zn^{2+} or Mg^{2+} (Alcolombri *et al*., 2017). Overall, the structure and function of DMSP-degrading enzymes mentioned above are summarized in Table 3.

Oxidation pathway. In the oxidation pathway, DMSP is oxidized to dimethylsulfoxonium propionate (DMSOP), which is further metabolized to dimethylsulfoxide (DMSO) and acrylate; however, enzymes involved in this pathway are unknown (Fig. 3) (Thume *et al*., 2018).

MeSH removal, DMSO reduction and DMS oxidation. MeSH can be modified by two pathways – MeSH S-methylase MddA or the MeSH oxidase MTO. The MTO enzyme, present in *Thiobacillus*, *Hyphomicrobium* and *Rhodococcus* species, oxidizes MeSH to generate formaldehyde (Suylen *et al*., 1987; Gould and Kanagawa, 1992; Kim *et al*., 2000; Lee *et al*., 2002; Eyice *et al*., 2018). MddA enzyme is reported in *Pseudomonas deceptionensis* $M1^T$ (Carrion *et al*., 2015; Carrion *et al*., 2017), and it is also found in many different aerobic and anaerobic bacteria, including cyanobacteria, and is known to methylate MeSH to produce DMS through a DMSP-independent pathway (Carrion *et al*., 2015). DMS is also produced through an alternate DMSP-independent pathway by the reduction of DMSO through DMSO reductase (DMSOR) enzyme reported in a few marine heterotrophic bacteria and in some bacteria found in anaerobic environments such as freshwater sediments (Griebler, 1997; Kappler and Schäfer, 2014). In bacteria, three key DMS-oxidizing enzymes – DMS dehydrogenase (DdhA), trimethylamine monooxygenase (Tmm), and DMS mono-oxygenase enzyme (DmoA) have been identified. DMS is oxidized by DdhA to yield DMSO in *Rhodovulum sulfidophilum* (McDevitt *et al*., 2002), or through Tmm in various Roseobacters and particularly SAR11 bacteria (Chen *et al*., 2011; Lidbury *et al*., 2016). Besides, there are some Alpha- and Beta-proteobacteria and Actinobacteria, which oxidize DMS by DmoA to yield MeSH (Visscher and Taylor, 1993; Borodina *et al*., 2000; Boden *et al*., 2011) (Fig. 4).

Genome context analysis of genes involved in DMSP production and catabolism

The genome context gives significant information about the enzymatic activity of DMSP lyase genes. The genome neighbourhoods of *dddD* gene are represented by proximal *dddB* and *dddC* genes, encoding an iron-containing dehydrogenase and a methyl-malonate semi-aldehyde dehydrogenase-like protein, respectively (Fig. S3B) (Todd *et al*., 2007; Curson *et al*., 2011a; Lei *et al*., 2018). 3-Hydroxypropionate-CoA produced by DddD enzyme is transformed into malonate semi-aldehyde by DddB and later to acetyl-CoA by DddC (Curson *et al*., 2011a). The putative acrylate using genes are present repetitively in

Table 3. Structural determination and features of the enzymes involved in DMSP catabolism.

Protein	Species	k_{cat}/K_M (M^{-1} s^{-1})	Crystallization	Cofactor	Key amino acid residue	PDB code	References
DMSP demethylation pathway							
DmdA	*Pelagibacter ubique*	618	Yes	THF	NA	3TFH	Reisch *et al*. (2008) and Schuller *et al*. (2012)
DmdB	*Ruegeria lacuscaerulensis* ITI_1157	NA	Yes	ATP HS-CoA	NA	6IHK/6IJB	Shao *et al*. (2019)
DmdC	*Roseovarius nubinhibens* ISM	NA	Yes	FAD	NA	6IJC	Shao *et al*. (2019)
DmdD	*Ruegeria pomeroyi*	5×10^6	Yes	NAD	NA	4IZB	Tan *et al*. (2013)
DMSP cleavage pathway							
DddP	*R. lacuscaerulensis* ITI_1157	NA	Yes	Fe^{3+}	Asp377	4RZY	Todd *et al*. (2009), Kirkwood *et al*. (2010a), and Wang *et al*. (2015)
DddQ	*R. lacuscaerulensis* ITI_1157	0.27	Yes	Zn^{2+} or Fe^{3+}	Tyr131 or Tyr120	4LA2 5JSO	Todd *et al*. (2011), Li *et al*. (2014), Brummett and Dey (2016), and Lei *et al*. (2018)
DddY	*Acinetobacter bereziniae*	1.66×10^6	Yes	Zn^{2+}	Tyr271	5XKX	de Souza and Yoch (1995) and Li *et al*. (2017)
DddX	*Psychrobacter sp*. D2	1.6×10^3	Yes	CoA	Glu432	NA	Li *et al*. (2021)
DddK	*P. ubique*	608	Yes	Ni^{2+}, Fe^{2+}, Zn^{2+}	Tyr64	5TFZ	Sun *et al*. (2016), and Schnicker *et al*. (2017)
DddD	*Marinomonas sp*. MWYL1	318	No	Acetyl CoA	NA	NA	(Alcolombri *et al*., 2014)
DddL	*Thioclava pacific*	NA	No	Mn^{2+}	NA	NA	Curson *et al*. (2008) and Lei *et al*. (2018)
DddW	*R. pomeroyi* DSS3	2.10×10^3	No	Fe^{2+} or Mn^{2+}	NA	NA	Todd *et al*. (2012), and Brummett *et al*. (2015)
Alma1	*Emiliania huxleyi*	0.8×10^5	No	Metal-independent	NA	NA	Alcolombri *et al*. (2015)

NA, Data not available/yet to be characterized.

dddY's genome neighbourhoods (Fig. S3C). Undoubtedly, *Desulfovibrio acrylicus* DddY (DaDddY) converts acrylate into propionate (van der Maarel *et al*., 1996; Curson *et al*., 2011b); and *A. faecalis* M3A strain that possesses AfDddY transforms the acrylate into 3-hydroxypropionate (Ansede *et al*., 1999). Nonetheless, the genome context is not conserved in DddL, and an *acuI*-like zinc-containing reductase is located adjacent to DddL in 4 out of 15 genomes (Fig. S3D) (Lei *et al*., 2018). In case of *dddK* genes in the genomes of SAR11, the closeness of enoyl-ACP-reductase, β-ketoacyl-ACP-synthase and β-hydroxydecanoyl-ACP dehydratase shows a relation to fatty acid or polyketide biosynthesis (Fig. S3E) (Massengo-Tiasse and Cronan, 2009; Sun *et al*., 2016; Lei *et al*., 2018). In case of *dddW* gene, the proximal D-alanyl-D-alanine carboxypeptidase gene indicates a gene cluster that is participating in bacterial peptidoglycan synthesis (Fig. S3F). The highly conserved genome neighbourhood of *dddQ* involves a putative mandelate racemase-like protein and a putative dimethylglycine dehydrogenase. These neighbours of *dddQ* indicate that DddQ participates in the degradation of proline-betaine and/or hydroxyproline-betaine. Thus, its DMSP lyase activity is expected to be promiscuous (Lei *et al*., 2018) (Fig. S3A). In *Psychrobacter sp*. D2, *dddT*, *dddB* and *dddC* are clustered with the DMSP lyase gene *dddX* (Fig. S4; Li *et al*., 2021). Gene neighbourhoods of *dmdA* in selected bacterial strains are shown in Fig. S4.

In many bacteria, the *dsyB* gene is located adjacent to genes with no related reported function of DMSP. In some Rhodobacterales strains, *dsyB* is closely associated to a isc/suf gene cluster, encode proteins involved in Fe–S cluster assembly. In Rhizobiales bacterium HL-109, *dsyB* is downstream of two genes encoding peroxiredoxins (Fig.S5) (Curson *et al*., 2018). Aminotransferase, dehydrogenase and decarboxylase are located adjacent to *mmtN* in many marine bacterial genomes (Fig.S6) (Williams *et al*., 2019).

Regulation of cleavage/demethylation in *R. pomeroyi* DSS-3

The water-column concentration of DMSP has been hypothesized to be a key factor regulating the choice of degradation pathway by bacteria (DMSP Availability Hypothesis) and it has been speculated that bacteria regulate the fate of sulfur from DMSP by adjusting the relative expression of the demethylation and cleavage pathways (bacterial switch hypothesis) (Kiene *et al*., 2000; Simó, 2001). Recently, single-cell measurements of the expression of demethylation and cleavage pathways using engineered fluorescent reporter strains of *R. pomeroyi* DSS-3 showed that external DMSP concentration induces an upregulation of both pathways, but only at high concentrations (>1 μM for demethylation; >35 nM for cleavage), characteristic of microscale

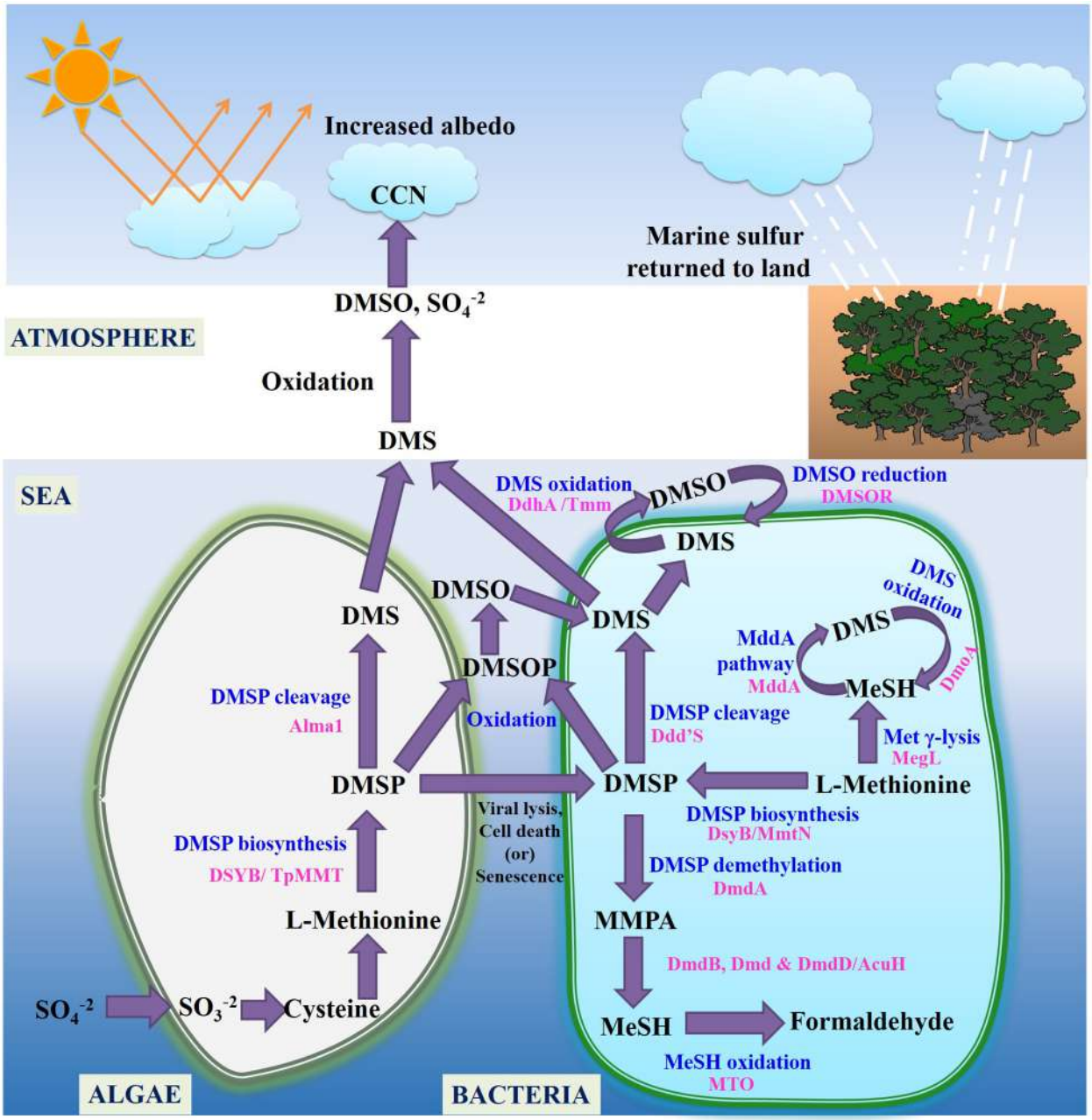

Fig. 4. Microbial biosynthesis and cycling of DMSP and DMS. AcuH, acryloyl-CoA hydratase; AlmA1, DMSP lyase; CCN, cloud condensation nuclei; Ddds, various DMSP lyases; DdhA, dimethylsulfide dehydrogenase; DmdA, DMSP demethylase; DmdB, MMPA-CoA ligase; DmdC, MMPA-CoA dehydrogenase; DmdD, methylthioacryloyl-CoA hydratase; DmoA, dimethylsulfide monooxgenase; DMS, dimethylsulfide; DMSO, dimethyl sulfoxide; DMSOR, dimethyl sulfoxide reductase; DMSP, dimethylsulfoniopropionate; DMSOP, dimethylsulfoxonium propionate; DsyB, DSYB; MddA, MeSH S-methyltransferase; MegL, Methionine γ-lyase; MeSH, methanethiol; MMPA, methylmercaptopropionate; MmtN, Met-methylating enzymes; MTO, MeSH oxidase; Tmm, trimethylamine monooxygenase; TpMMT, methylthiohydroxybutryrate SAM-dependent methyltransferase.

hotspots such as the vicinity of phytoplankton cells. Rather than expressing only one pathway at any given DMSP concentration, it has been observed that bacteria regulate both pathways in concert but adjust the ratio of cleavage and demethylation according to DMSP concentration (Gao *et al*., 2020).

DMSP uptake

Prokaryotic phytoplankton from the groups *Prochlorococcus*, *Synechococcus*, as well as some eukaryotic phytoplankton from the dinoflagellates, cryptophytes and diatoms groups, and heterotrophic bacteria have been shown to take up dissolved DMSP (Vila-Costa *et al*., 2006; Spielmeyer *et al*.,

2011; Ruiz-González *et al*., 2012; Petrou and Nielsen, 2018). However, to date, the proportion and magnitude of DMSP taken up by phytoplankton in natural communities remain unclear. Recently, the uptake of DMSP by different fractions of marine microbial communities between the two sites (outer site and inner site) within Great Barrier Reef (GBR), Australia shows that both non-DMSP producing phytoplankton and bacteria can uptake DMSP from natural reef waters over short time scales. Specifically, DMSP enrichment showed the dominant sink for DMSP was taxa from the largest microbial fraction (>8 μm). It was proposed that the dinoflagellates accounted for the high proportion of particulate DMSP in the >8 μm fraction, but that the major taxa accountable for the uptake of additional DMSP in the +DMSP treatment be attributed to the diatoms, which accumulated DMSP in high concentrations (Petrou and Nielsen, 2018; Fernandez *et al*., 2021). At the outer reef site, the absence of diatoms suggested that other large non-DMSP producing phytoplankton might act as DMSP sinks, but further work is needed to confirm uptake and identify these groups. Longer-term incubations revealed, however, that DMSP retention was short-lived (<24 h) and microbial responses to DMSP enrichment varied between the two sites within GBR. For bacterial fractions, it was suggested that at the inner reef site sulfur and carbon demands were largely met by existing DMSP availability and lyase activity dominating the conversion of DMSP to DMS. On the other hand, communities from the outer reef were sulfur and carbon limited, and it was presumed that any DMSP in the outer reef was being converted to MeSH or lost from the system via oxidation when taken in the context of the low DLA (DMSP lyase activity) rates measured (Fernandez *et al*., 2021). At both sites, the most abundant DMSP degrading pathway was demethylation, represented by the gene DmdA (Dall and A1) and DddP lyase was approximately twice as abundant in the bacterial population of the inner reef in comparison to the outer reef. Among the bacterioplankton, the groups most likely to demethylate DMSP in these water were SAR11 and members of the Rhodobacterales (Howard *et al*., 2008; Fernandez *et al*., 2021). However, as SAR11 were more abundant than Rhodobacterales at both reef sites, it has been speculated that they may form the dominant DMSP consumer in the surface waters of the GBR. Currently, it has been hypothesized that the phytoplankton DMSP lyase activity measure in these GBR waters is likely attributable to the high DMSP-producing dinoflagellates at both sites (Fernandez *et al*., 2021).

DMSP transport

Structurally, DMSP is a zwitterion and this charge means that it cannot cross cell membranes without a specific transporter (Kiene *et al*., 1998). There are two main families of the transporter that are known to be used by the bacteria *Roseobacter*, SAR11 clade bacteria, cyanobacteria, and also phytoplankton (Dickschat *et al*., 2015) to transport DMSP into the cell for use and catabolism. One of the transporter types proposed to be utilized by DMSP is the betaine choline carnitine transporter (BCCT) (Ziegler *et al*., 2010), which are associated with *dddD* and several other catabolic genes within various species (Curson *et al*., 2011a). These transporters exist almost ubiquitously in microorganisms, and, as the name suggests, are known to transport glycine betaine across the membrane in species such as *Escherichia coli* (Dickschat *et al*., 2015). The nomenclature and amino acid sequences of BCCT transporters vary between species, ranging from CaiT in *E. coli* to BetP in *Corynebacterium glutamicum* (Sun *et al*., 2012), and DddT in both *Marinomonas* (Todd *et al*., 2007) and *Halomonas* HTNK1 (Todd *et al*., 2010). The marine halophile *Vibrio parahaemolyticus* contains four BCCT carriers (BccT1 to BccT4). It is indicated that BccT1 and BccT2 are carriers of DMSP in *V. parahaemolyticus*, whereas BccT3 and BccT4 do not play a significant role in DMSP transport in *V. parahaemolyticus* (Gregory *et al*., 2020). Of the four additional *Vibrio* species that used DMSP as an osmolyte, *V. harveyi* and *V. fluvialis* contain homologues of BccT1 and BccT2 while *V. vulnificus* and *V. cholerae* can utilize DMSP as an osmolyte and contained only a BccT3 homologue. In *V. vulnificus* strains, an additional BCCT family transporter, named BccT5, was also a carrier for DMSP (Gregory *et al*., 2020). The second transporter family found to carry DMSP across the membrane is the ATP binding cassette (ABC) transporter, a commonly used primary transporter that can be found in all three domains of life (Eitinger *et al*., 2011). More recently, the Gram-positive bacterium *Bacillus* was shown to utilize DMSP as an osmoprotectant by uptake via the ABC family transporters OpuC and OpuF (Broy *et al*., 2015; Teichmann *et al*., 2018). Currently, the *Clostridioides difficile* CDIF630erm_01020/01021 operon clearly encodes a compatible solute transporter OpuF. This ABC transporter preferentially transports homobetaine, proline betaine, DMSP, γ-butyrobetaine and glycine betaine (Michel *et al*., 2022). Another example of this type of transport is the DMSP transporter encoded for by the *potABCD* genes in *Burkholderia ambifaria* (Dickschat *et al*., 2015). The genes encoding many of these ABC transporters, like the BCCT transporters, have been linked to the *dddD* gene in multiple species (Sun *et al*., 2012).

Concluding remarks

DMSP and DMS play crucial role in driving the global sulfur cycle and may influence local weather. DMSP

synthesis and degradation have been reported in both marine prokaryotes and eukaryotes. Research in exploring DMSP synthesis and catabolism by various DMSP lyases is still ongoing. The global distribution pattern of DMSP and DMS, the known genes for biosynthesis and cleavage of DMSP, and the physiological and ecological functions of these important organosulfur molecules have been reviewed (Zhang *et al*., 2019). Various sulfur metabolites, including DMSP release and uptake from the dissolved organic matter pool by marine microorganisms, and the ecological links facilitated by their diversity in structures, oxidation states and chemistry have been recently reviewed (Moran and Durham, 2019). However, this article will enhance our knowledge about the DMSP biosynthesis and catabolism in various organism particularly the genes and mechanism of action of several corresponding enzymes involved. The recent reports on DMSP synthesis enzymes DsyB in marine Alphaproteobacteria *L. aggregata* LZB033, DSYB in many phytoplankton and corals, TpMMT in the diatom *T. pseudonana* and MmtN in the bacterium *Novosphingobium* BW1 suggest the presence of different enzymes involved in DMSP biosynthesis in different group of marine organisms. Further the molecular mechanisms involved in DMSP synthesis in DMSP-producing organisms that lack *dsyB*/*mmtN* or *DSYB*/*TpMT2* are to be explored in detail for in-depth understanding of the molecular 'pathway'. Moreover, it is imperative to study DMSP production across a wide range of sea environments ranging from deep-sea sediments to pelagic zones. Recently, it has been reported that many other Gram-positive actinobacteria can make DMS from DMSP but lack known DMSP lyase genes (Liu *et al*., 2018). Thus, there is still more biodiversity involved in microbial DMSP lyases, which needs to be uncovered. Many marine bacteria, especially Roseobacters, are reported to metabolize DMSP via more than one pathway. For instance, *R. pomeroyi* DSS-3 contains both the demethylation and the lysis pathway. Moreover, it possesses multiple DMSP lyases (DddP, DddQ and DddW). Why some bacteria have evolved multiple DMSP utilization pathways and some bacteria only possess one pathway awaits further investigation. The functions of DMSP and DMS in marine microorganisms have to be verified at the molecular and genetic levels. The crystal structure and mechanism of DMSP cleavage of some DMSP lyase enzymes such as DddD, DddL, DddW and Alma1 are yet to be solved.

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Author contributions

D.S. conceptualized and drafted the manuscript. Both authors J.S. and P.V.R. read, edited, and approved the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1. Neighbour-joining phylogenetic tree of MmtN proteins. Taxonomic groups are indicated with various colours – Actinobacteria-light blue; Alphaproteobacteria-green; Deltaproteobacteria-red; Gammaproteobacteria-blue; and Unclassified bacteria-purple. The shaded colours indicates functional proteins. Bootstrap support for nodes is marked.

Fig. S2. A-Proposed DMSP biosynthesis in *Burkholderia thailandensis* B-The bur biosynthetic gene cluster in *B. thailandensis*

Fig. S3. The genomic context of DddQ, DddD, DddY, DddL, DddK and DddW (Lei *et al*., 2018). The genes encoding orthologs are highlighted with the same colour. For (A) DddQ; (B) DddD; (C) DddY; (D) DddL; (E) DddK; and (F) DddW in different bacteria genome.

Fig. S4. Gene neighbourhoods of DddX (A) and DmdA (B) (Landa *et al*., 2019; Li *et al*., 2021).

Fig. S5. Gene maps showing genomic locations of *dsyB* in selected *dsyB*-containing bacteria (Curson *et al*., 2017). (A) Gene map for *Labrenzia aggregata* LZB033 and *L. aggregata* IAM12614. Predicted gene products: 1. tricarboxylate transporter; 2. AraC family transcriptional regulator; 3. nucleotide phosphate sugar epimerase; 4. hypothetical protein; 5. dehydratase; 6. MaoC-like dehydratase; 7. hypothetical protein; 8. agmatinase; 9. acetyltransferase; 10. cob(II)yrinic acid a,c-diamide reductase; 11. adenine phosphoribosyltransferase; 12. S-methyladenosine phosphorylase; 13. hypothetical protein; 14. cytochrome C1. (B) Gene map for *Salipiger mucosus* DSM16094 and *Pelagibaca bermudensis* HTCC2601. Genes encoding protein products predicted to be involved in Fe-S cluster assembly are marked. Predicted gene products: 1. cysteine desulfurase; 2. hypothetical protein; 3. hypothetical protein; 4. SufD Fe-S cluster assembly protein; 5. SufC Fe-S cluster assembly ATP-binding protein; 6. SufB iron-regulated ABC transporter membrane component; 7. cysteine desulfurase; 8. BadM/Rrf2 family transcriptional regulator; 9. Transposase. (C) Gene map for *Rhizobiales* bacterium HL-109. Predicted gene products: 1. serine protease; 2. DNA polymerase; 3. acetyltransferase; 4. peroxiredoxin; 5. peroxiredoxin; 6. uncharacterized membrane protein; 7. hypothetical protein; 8. tyrosine phosphatase; 9. outer membrane immunogenic protein.

Fig. S6. Gene maps showing genomic locations of *mmtN* in selected *mmtN*-containing bacteria (Williams *et al*., 2019).