



Chemical Diversity and Biochemical Transformation of Biogenic Organic Sulfur in the Ocean

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Organic sulfur compounds are not only essential for organismal survival but also indispensable for the sulfur cycle. Over the past few decades, dimethylsulfoniopropionate (DMSP) and dimethyl sulfide (DMS) cycling in the upper ocean have been well characterized from the genetic to the ecosystem level. Recent advances in the study of marine sulfonate transformation have indicated that phytoplankton and microbes play key roles in oceanic sulfur and carbon fluxes. This review provides biochemical details of the major sulfur metabolites, and presents an interlinked reaction network with genetic information on the microbial transformation and mineralization of sulfur compounds. This review also discusses future prospects for the discovery and characterization of novel substrates and enzymes involved in organosulfur cycling, as well as for investigations of deep sea and sedimentary organic sulfur.

Keywords: **microbe, organic sulfur, gene, sulfur cycle, transformation**

Abbreviations: γ -Glu-Cys, γ -glutamylcysteine; Alma1, DMSP lyase in *Emiliania huxleyi*; aprAB, adenylyl-sulfate reductase; APS, adenosine 5'-phosphosulfate; betC, choline-sulfatase; CFB, Cytophaga-Flavobacteria-Bacteroides; comA, phosphosulfolactate synthase; comC or slcC, sulfolactate dehydrogenase; comD, sulfopyruvate decarboxylase subunit alpha; comE, sulfopyruvate decarboxylase subunit; cuyA, L-cysteate sulfo-lyase; cyaS, cysteate synthase; Cys, cysteine; cysC, adenylyl-sulfate kinase; cysH, phosphoadenosine phosphosulfate reductase; cysJ, sulfite reductase alpha-component; cysK/cysM, cysteine synthase A/B; dcyD, cysteine desulphydrase; ddd, DMSP lyases (including dddD, dddK, dddL, dddP, dddQ, dddY, and dddW); DHPS, 3-sulfopropanediol; dmdA, DMSP demethylase; DMS, dimethyl sulfide; DMSO, dimethylsulfoxide; DMSOP, dimethylsulfoxonium propionate; DMSP, dimethylsulfoniopropionate; DOS, dissolved organic sulfur; dsrAB, reversible dissimilatory sulfite reductase; DYSB/dysB (eukaryotic/prokaryotic gene name), 4-methylthio-2-hydroxybutyrate methyltransferase; FT-ICR-MS, Fourier transform ion cyclotron resonance mass spectrometry; GALNS, N-acetylgalactosamine-6-sulfatase; GNS, N-acetylglucosamine-6-sulfatase; GSH, glutathione; GSSG, glutathione disulfide; hpsO, hpsP and hpsN, DHPS hydrogenase enzymes; mdeA, methionine γ -lyase; MeSH, methanethiol; Met, methionine; metY, O-acetylhomoserine sulfhydrylase; metY1, O-acetylhomoserine; metZ, O-succinylhomoserine sulfhydrylase; MSA, methanesulfonate; MSA, methanesulfonate; msmA, methanesulfonate monooxygenase subunit alpha; mstA, 3-mercaptoproprylate sulfurtransferase; MTHB, 4-methylthio-2-hydroxybutyrate; mtoX, methanethiol oxidase; mtsA, methylated-thiol-coenzyme M methyltransferase; PAPS, 3'-phosphoadenosyl-5'-phosphosulfate; raprA, reverse-type adenylyl-sulfate reductase subunit alpha; raprB, reverse-type adenylyl-sulfate reductase subunit beta; rdsVA, reverse-type dissimilatory sulfite reductase subunit A; sat/cysD, sulfate adenylyltransferase; sir, ferredoxin-sulfite reductase; soeA, sulfate dehydrogenase subunit SoeA; soxC, Sulfur dehydrogenase subunit SoxC; SQ, sulfoquinovose; sqdA, UDP-sulfoquinovose acyltransferase; sqdB, UDP-sulfoquinovose synthase; SQDG, sulfoquinovosyldiacylglycerol; sqr, sulfide-quinone reductase; ssuD, alkanesulfonate monooxygenase; suyAB, (2R)-sulfolactate sulfo-lyase; suyB, (2R)-sulfolactate sulfo-lyase subunit beta; tauD, taurine dioxygenase; UDP, uridine diphosphate; xsc, sulfoacetaldehyde acetyltransferase; yihQ, sulfoquinovosidase.

INTRODUCTION

Sulfur is an essential component of all life forms. Over the past three decades, our understanding of the transformation of inorganic sulfur species with oxidation states ranging from -2 to $+6$ in the marine environment has dramatically improved, including the microbial oxidation, reduction, or disproportionation of sulfide (S^{2-}), elemental sulfur (S^0), polysulfides (S_n^{2-}), thiosulfate ($\text{S}_2\text{O}_3^{2-}$), sulfite (SO_3^{2-}), and sulfate (SO_4^{2-}) (Friedrich et al., 2001; Pro et al., 2007; Klotz et al., 2011). In the ocean, most sulfur is present as inorganic sulfate (approximately 28–29 mM) (Canfield and Farquhar, 2009). Because phytoplankton and microbes assimilate inorganic sulfate into the amino acid cysteine (Cys) and methionine (Met) (Kiene et al., 1999), organic sulfur metabolism is ubiquitous in living organisms. Organic sulfur compounds constitute the major sinks for sulfate in the ocean; these include dissolved and particulate sulfur compounds in seawater, and biomass sulfur generated by phytoplankton and microbes (Ksionzek et al., 2016). The biomineralization and recycling of organic sulfur are critically important for the sustainment of the sulfur cycle. The fundamental biogeochemical processes of organic sulfur have been described in detail elsewhere (Moran and Durham, 2019). This review summarizes current knowledge of the chemistry and biochemistry of sulfur metabolites in the ocean, and constructs a sulfur metabolic network using reaction data cataloged in the MetaCyc database (Caspi et al., 2018). Next, the genetic capabilities of marine microbes with respect to the transformation and mineralization of organic sulfur are examined using a publicly available genomic database, as well as the *Tara Oceans* metagenomic datasets (Sunagawa et al., 2015). The review also discusses the prospective future chemical, biochemical and biogeochemical studies of organic sulfur compounds.

CHEMICAL DIVERSITY AND REDOX ACTIVITY OF BIOGENIC ORGANIC SULFUR

Sulfur is found in various organic molecules in the cell, including amino acids, lipids, carbohydrates, coenzymes, cofactors, vitamins, steroids, and secondary metabolites. More than 20 sulfur-containing functional groups are present in biogenic organic compounds (Figure 1 and Supplementary Table S1). Sulfur in organosulfur compounds can be directly linked to the carbon chain (e.g., the sulfonate moiety, $-\text{C}-\text{SO}_3$), or can be attached to either an oxygen atom (e.g., sulfate ester, $-\text{O}-\text{SO}_3$) or a nitrogen atom (e.g., sulfonamide, $-\text{NH}-\text{S}-$). As Supplementary Table S1 shown, the most abundant class of sulfur compounds is thioether ($-\text{S}-$), followed by sulfate ester, thioester [$-(\text{O})\text{C}-\text{S}-$], thiol ($-\text{SH}$), sulfonates, sulfoxide ($-\text{SO}$), disulfide ($-\text{S}-\text{S}-$), and sulfonium ($[\text{R}_3\text{S}]^+$) classes.

Sulfur in organosulfur compounds exists in several oxidation states, ranging from -2 to $+6$, and undergoes formal oxidation state transformations via electron transfer, hydrogen atom transfer, radical processes, and exchange reactions (Figure 1

and Supplementary Table S1). The distinct redox properties of sulfur species ensure that they play vital roles within a cell, including antioxidation and maintenance of the redox state (Jacob and Anwar, 2008). The compounds containing sulfur in its most reduced state (-2) represent the largest part of the overall antioxidant pool in cells, which include Cys, Met, glutathione (GSH, L- γ -glutamyl-L-cysteinyl-glycine), dimethylsulfoniopropionate (DMSP), and dimethyl sulfide (DMS) (Sunda et al., 2002; Fahey, 2013; Mukwewho et al., 2014). An antioxidant role for DMSP is further supported based on evidence that this compound can be oxidized to dimethylsulfoxonium propionate (DMSOP, a sulfur atom with an oxidation state of 0) (Figure 1) (Thume et al., 2018). Compounds containing more oxidized forms of sulfur also have antioxidative properties, including dimethylsulfoxide (DMSO, sulfoxide, 0) and taurine (sulfonate, +4) (Figure 1).

MAJOR BIOGENIC ORGANIC SULFUR COMPOUNDS IN THE OCEAN

Dissolved organic sulfur (DOS) concentrations are generally around 200–300 nM in oceanic surface waters, and decrease with depth to approximately 160–200 nM in bathypelagic waters (Ksionzek et al., 2016). Phytoplankton was estimated to assimilated $\sim 1,360$ Tg S/year (1 Tg = 10^6 tons) into organic matter and support a major fraction of sulfur flux in the surface ocean (Ksionzek et al., 2016). Sulfate is converted into organic matter by phytoplankton, including proteins (~35%), sulfate esters (~21%), sulfolipids (~4%) and other low-weight compounds (~40%) (Bates et al., 1994; Giordano et al., 2005). Sulfur metabolites are part of the molecules exchanged between phytoplankton and marine microbes (Seymour et al., 2017). For example, heterotrophic bacteria can utilize phytoplankton-derived DOS such as DMSP, 3-sulfopropanediol (DHPS), sulfur-containing cofactors vitamin B1 and B7 for growth requirement and can produce secondary metabolite such as tropodithietic acid, which is thought to protect the algal growth (Wang et al., 2016). Clearly, many different organic sulfur biosynthesis contributes to the pool of sulfur in the marine environment. Of those compounds, sulfur-containing amino acids and derivatives, methyl-sulfur compounds, sulfonates and sulfate esters as the primary sulfur sources are rapidly cycled by the upper-ocean planktonic microbes (Figure 1), and have low concentrations in water columns (commonly in the nanomole range per liter) (Moran and Durham, 2019). Those naturally occurring organic sulfur available to microbes as sources of sulfur or carbon are described below.

Sulfur-Containing Amino Acids and Derivatives

The sulfur-containing amino acid Cys and Met contain thiol and thioether functional groups, respectively. Apart from their function as a structural component of proteins, Cys and Met also plays fundamental roles in cellular metabolism. Cys is a precursor for biomolecules such as L-homocysteine, coenzyme A and GSH (Vermeij and Kertesz, 1999). Met is

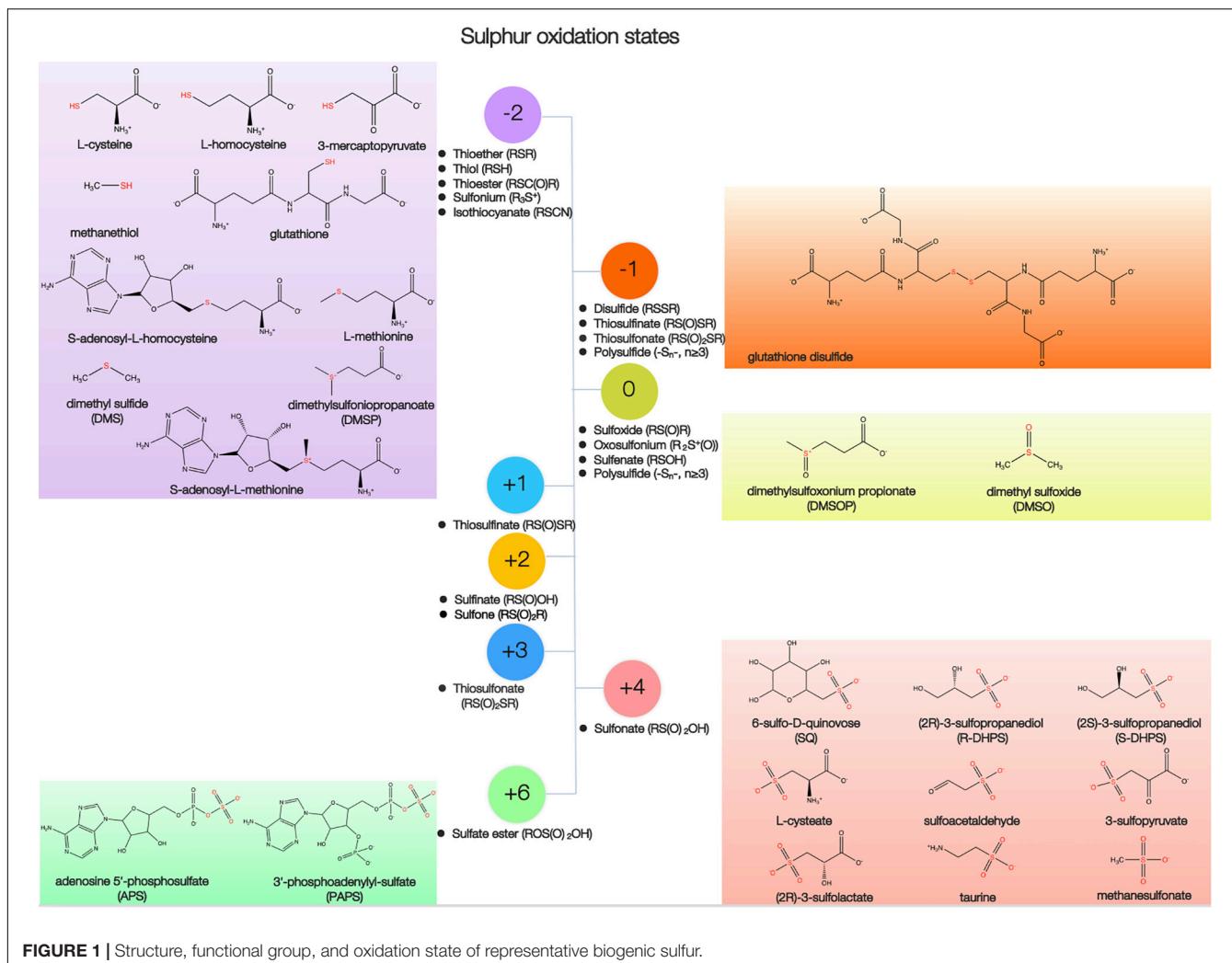


FIGURE 1 | Structure, functional group, and oxidation state of representative biogenic sulfur.

an initiator of protein synthesis and a precursor in many metabolic processes, such as methylation and formylation via its derivatives *S*-adenosyl-L-homomethione and *N*-formyl methionine-tRNA, respectively (Ferla and Patrick, 2014). The intracellular free Cys, Met, L-homocysteine, and *S*-adenosyl-L-homomethione in bacteria are maintained at low (sub-millimolar) levels but are sufficient for protein synthesis and production of essential metabolites (Bennett et al., 2009). GSH, one of the most abundant naturally occurring thiols, is the major antioxidant found in many organisms in millimolar concentration (Bennett et al., 2009; Fahey, 2013). Thiol compounds, such as Cys and GSH, may bind metal ions and thus increase the uptake of metal by marine phytoplankton (Ahner et al., 2002; Walsh et al., 2015). Glutathione disulfide (GSSG) is also present in cells in millimolar concentration (Bennett et al., 2009), which is formed as a result of GSH oxidation. In conjunction with GSH, GSSG helps to prevent oxidative damage and detoxify harmful substances (Diaz et al., 2019).

Concentrations of dissolved thiol are commonly ~10 nM in the open ocean, but can be larger in regions of high productivity

(Al-Farawati and van den Berg, 2001; Dupont et al., 2006). Cys, GSH, and γ -glutamylcysteine (γ -Glu-Cys) are the low-molecular-weight thiols that are frequently detected in the marine environments (Dupont et al., 2006). GSH is the most abundant particulate thiol in the ocean, while Cys and γ -Glu-Cys are primarily found dissolved (Dupont et al., 2006). Dissolved γ -Glu-Cys concentrations up to 15 nM have been measured in the northeast Pacific Ocean (an area of high productivity); in this region, Cys and GSH concentrations ranged from below detection limits (~0.01 nM) up to 1 nM, consistent with levels reported in other ocean regions (Swarr et al., 2016). Previous estimates of dissolved Met concentrations ranged from 0.01 to 1 nM in surface waters (Valle et al., 2015). However, Cys and Met in dissolved combined amino acids is 10–100 more abundant than dissolved free ones.

Methyl-Sulfur Compounds

The sulfonium compound DMSP is a secondary metabolite; abundant DMSP concentrations are produced and stored by micro- and macroalgae (Curson et al., 2018). DMSP may function as a compatible solute, a cryoprotectant, an

antioxidant, or a chemoattractant, and may also act as transient pool for excess intracellular sulfur (Kiene et al., 2000; Sunda et al., 2002; Yoch, 2002; Otte et al., 2004; Seymour et al., 2010). Approximately one billion tons of DMSP is generated annually by marine phytoplankton (Gali et al., 2015). DMSP concentrations in diatom cells are typically 1–50 mM, while DMSP concentrations in dinoflagellate and coccolithophore cells are typically 100–300 mM (Matrai and Keller, 1994; Ho et al., 2003). Concentrations of dissolved DMSP are typically 0.5–3 nM in the open ocean, but dissolved DMSP is occasionally measured at high concentrations (>100 nM) (Kiene and Slezak, 2006; Jarníková et al., 2018). In addition, particulate DMSP concentrations are consistently higher than dissolved DMSP concentrations in field samples (Archer et al., 2001; Kiene and Slezak, 2006). The concentrations of particulate DMSP were up to 4,240 nM during a massive bloom of the dinoflagellate *Akashiwo sanguinea* in estuarine waters, however, the extracellular dissolved DMSP remained below 7.2 nM due to microbial consumption (Kiene et al., 2019).

DMSP is a globally important substrate in the sulfur cycle as it is the precursor of the DMS (Simó, 2001; Yoch, 2002), methanethiol (MeSH) (Curson et al., 2011b), DMSO and DMSOP (Thume et al., 2018). DMS is the main source of biogenic sulfur in the atmosphere, and may influence the Earth's climate due to its atmospheric oxidation products, which form cloud condensation nuclei (Andreae and Crutzen, 1997; Barnes et al., 2006). Approximately 10^7 tons of DMS are produced annually, with a typical sea surface concentration of 1–7 nM (Kloster et al., 2006; Lana et al., 2011; Alcolombri et al., 2014). It was estimated that approximately 25–70% of DMS flux is oxidized to methanesulfonate (MSA, $\text{CH}_3\text{SO}_3\text{H}$), which is the most abundant biogenic sulfur compound in the atmosphere (Barnes et al., 2006). DMSP degradation may yield MeSH, a reduced sulfur source that may potentially provide 30–100% of the total sulfur demand of marine bacteria (Curson et al., 2011b). Intracellular concentrations of MeSH in diatoms and dinoflagellates vary from ~ 0.1 mM–1 mM (Giordano et al., 2005). MeSH concentrations are uniformly low in the open ocean (~ 1 nM) and decline with depth (Henriques and Marco, 2015). DMSO may protect algal cells from photo-generated oxidants and cryogenic damage (Lee and De Mora, 1999). DMSO represents another pool of dissolved dimethylated sulfur in seawater, with concentrations of ~ 1 –10 nM (Vila-Costa et al., 2008). DMSOP concentrations are much lower than DMSO concentration; average DMSOP concentration in coastal marine waters is 0.14 nM (Thume et al., 2018).

Sulfonates

Sulfonates have a sulfonic acid group covalently attached to carbon, and are generated by plants, animals, and the microbial conversion of inorganic sulfate (Kertesz, 1999). Chirality is common among sulfonates (Figure 1). Sulfoquinovose (SQ) is a sulfonated hexose with a stable carbon-sulfur bond (Figure 1) (Goddard-borger and Williams, 2017). SQ is considered one of the most abundant sulfur compounds in the biosphere

following Cys and Met, with an estimated annual global production of approximately 10^{10} tons (Goddard-borger and Williams, 2017). SQ is the polar head group of the plant sulfolipid sulfoquinovosyldiacylglycerol (SQDG) in variety of photosynthetic membranes from marine cyanobacteria (*Synechococcus* and *Prochlorococcus*) bacteria and algae (Goddard-borger and Williams, 2017), as well as of the cell wall in the Archaea (Palmieri et al., 2013). SQDG may maintain anionic charge homeostasis in the cell membrane by acting as a phosphatidylglycerol lipid substitute under very low phosphate availability conditions (Van Mooy et al., 2006). Concentrations of SQDG in the phosphate-depleted Sargasso Sea and in the South Pacific were $0.8 \mu\text{g liter}^{-1}$ and $0.3 \mu\text{g liter}^{-1}$, respectively (Van Mooy et al., 2009).

Besides SQDG, SQ is also the precursor for the synthesis of DHPS (Roy et al., 2003; Denger et al., 2014). The three-carbon (C_3) component of sulfonates, including DHPS, sulfolactate, sulfopyruvate and cysteate (Figure 1), as well as the C_2 -sulfonates taurine and sulfoacetaldehyde (Figure 1), is found in marine organisms (Goddard-borger and Williams, 2017). DHPS has been hypothesized to perform osmotic pressure or redox balancing in cells (Götz et al., 2018; Williams and Todd, 2019). High concentrations of DHPS can accumulate within diatom and coccolithophore cells in the millimolar range, on a scale comparable with that of DMSP (Durham et al., 2019). Furthermore, the concentration of particulate DHPS at multiple coastal sites was shown to actually exceed that of particulate DMSP (Durham et al., 2015). Most phytoplankton and cyanobacteria contained micromolar concentrations of cysteate, which can be formed in the oxidation of cysteine (Durham et al., 2019). Taurine, an amino sulfonic acid, has many biological roles in the cell, including bile acid chelation, osmoregulation, and membrane stabilization (Lambert et al., 2015). Taurine is widely produced by marine metazoans and some phytoplankton at intracellular concentrations that may exceed 200 mM (Visscher et al., 1999; Tevatia et al., 2015; Clifford et al., 2017). In the North Atlantic Ocean, taurine concentrations were ~ 0.1 –10 nM in epipelagic waters, and ~ 0.01 –1 nM in bathypelagic waters (Clifford et al., 2019).

Sulfate Esters

Besides sulfonates, sulfate esters are common forms of sulfur present in the marine sediments (Kertesz, 1999). Furthermore, a number of sulfate esters in marine organisms are known, ranging from aliphatic sulfate to sulfated polysaccharides (Kertesz, 1999; Kellner Filho et al., 2019). Sulfated polysaccharides are primarily found in marine eukaryotes: as fucoidan, ulvans, carragenans, agarans, or mucin in marine algae, and as chondroitin sulfate or heparan sulfate in marine invertebrates (Jiao et al., 2011; Wang et al., 2014). Fucoidan and ulvans usually constitutes about 5–10% of the dry biomass of brown algae and 15–65% of the dry biomass of green algae, respectively (Holdt and Kraan, 2011; Cunha and Grenha, 2016). Sulfated polysaccharides are located at the cell wall, on the cell surface, in the extracellular matrix, or within the intracellular compartment, and are primarily involved in cell growth, differentiation, adhesion, signaling, and extracellular matrix interactions (Jiao et al., 2011).

BIOCHEMICAL REACTION NETWORK FOR ORGANIC SULFUR

To understand the fate and transformations of organic sulfur compounds listed above in organisms, a sulfur metabolic network was constructed using reaction data cataloged in the MetaCyc database (Caspi et al., 2018). The sulfur metabolic map consisted of nodes, representing 432 sulfur metabolites (**Supplementary Table S1**), and edges, representing 1,598 enzymatic reactions (**Supplementary Table S1**). This network described the transfer of sulfur among organic compounds (**Figure 2**). Nodes with many connectors can be considered putative metabolic hubs. At these locations, many metabolic processes occur, enabling substances such as reaction intermediates to transfer between reaction processes on an as-needed basis. The sulfur metabolite hubs were generated by the most widespread, essential biochemical processes linked to sulfur-containing amino acid biosynthesis (Cys, Met, L-homocysteine, S-adenosyl-L-homocysteine, and S-adenosyl-L-homomethione), sulfate reduction (3'-phosphoadenosyl-5'-phosphosulfate, PAPS), and antioxidant agent biosynthesis (GSH and GSSG) (**Figure 2**).

The most widespread mechanism of sulfur assimilation into biomass is the sulfate reduction pathway. However, this pathway is energetically costly compared to the nitrate assimilation pathway, consuming 732 kJ mol^{-1} instead of 347 kJ mol^{-1} (Leustek and Saito, 1999). Methyl-sulfur compounds and sulfonates are generated by other critical sulfur-reducing transformation pathways (**Figure 2**). The complete DHPS desulfonation pathway converts sulfonates to sulfite (Mayer et al., 2010), an intermediate in the sulfate reduction pathway. These pathways provide a mechanism by which microorganisms can generate reduced sulfur from organic matter in order to satisfy cellular growth requirements, instead of depending on sulfate- or sulfur-containing amino acids as sulfur sources.

Sulfur-Containing Amino Acids and Derivatives Metabolisms

Microorganismal sulfate assimilation classically revolve around the activation and reduction of sulfate to sulfide, the incorporation of reduced sulfur into Cys, and the transfer of reduced sulfur from Cys into the downstream metabolites such as L-homocysteine, Met and GSH (**Figure 2**). Adenosine 5'-phosphosulfate (APS) and PAPS contain sulfate ester functional groups (**Figure 2**), which are key intermediates in the primary assimilation of sulfate into Cys (Klaassen and Boles, 1997). APS is synthesized via the adenylation of sulfate by sulfate adenylyltransferase (sat/cysD), a metabolic branchpoint in the sulfate reduction pathway (**Figure 2**). In the canonical microbial assimilatory sulfate reduction pathway, APS is phosphorylated by APS kinase (cysC) to generate PAPS, PAPS is reduced to sulfide, and organic sulfur compounds are biosynthesized by PAPS reductase and assimilatory sulfite reductases (**Figure 2**). However, APS can also be reduced to sulfite by adenylyl-sulfate reductase (aprAB) and further reduced to sulfide for energy purposes by reversible dissimilatory sulfite reductase (dsrAB) in the dissimilatory sulfate reduction pathway (**Figure 2**).

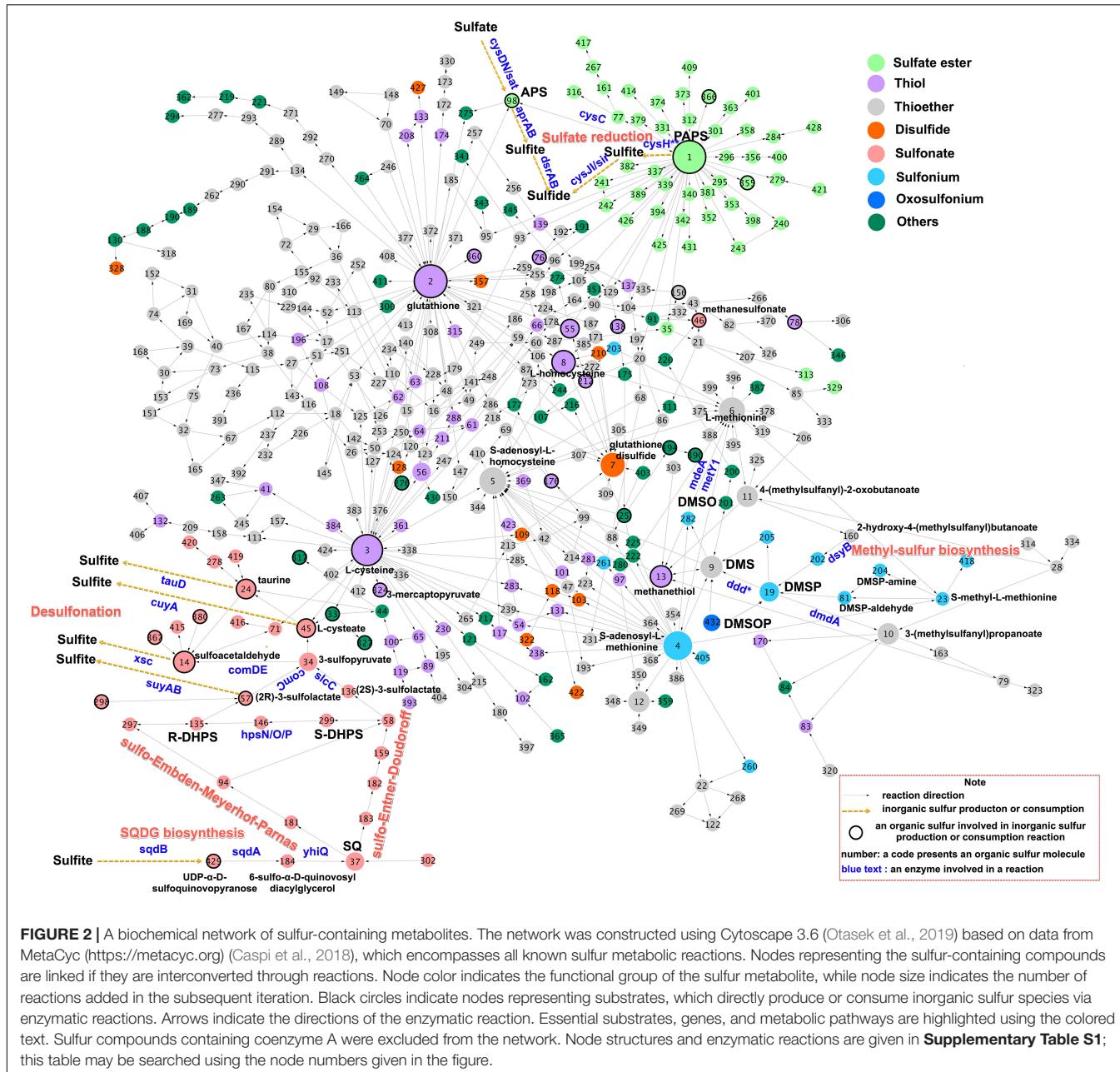
Met can be synthesized from homoserine and Cys via a transsulfuration pathway, which produces an intermediate metabolite L-homocysteine (Vermeij and Kertesz, 1999; Ferla and Patrick, 2014). Homocysteine can also be produced directly from sulfide and acylhomoserine by an *O*-acylhomoserine sulfhydrylase (metY) (Hacham et al., 2003). The conversion Met to Cys involves the synthesis of L-homocysteine via S-adenosyl-L-methionine and S-adenosyl-L-homocysteine (Wheeler et al., 2005). Cys is generally the rate-limiting substrate for GSH synthesis (Lu, 2013), in turn, GSH can be broken down by peptidases to give Cys (Suzuki et al., 2001). The major catabolic pathways of Cys are the transamination pathway and the direct oxidation pathway, finally yielding 3-mercaptoproprylate and cysteate, respectively (Christophersen and Anthoni, 1986). Met can be directly catabolized to MeSH by a methionine γ -lyase (mdeA) (Amarita et al., 2004), showing that sulfur-containing amino acids themselves serve as precursors of methyl-sulfur and sulfonate compounds.

Methyl-Sulfur Compounds Metabolisms

The biochemical and genetic mechanisms of DMSP biosynthesis and degradation have been reviewed in detail elsewhere (Moran et al., 2012; Bullock et al., 2017). Briefly, the biosynthesis of DMSP from Met by phytoplankton may proceed along a transamination pathway, a methylation pathway, or a decarboxylation pathway (Stefels, 2000). In the transamination pathway, Met first undergoes transamination to 4-methylthio-2-oxobutyrate, is then reduced to 4-methylthio-2-hydroxybutyrate (MTHB), followed by S-methylation to 4-dimethylsulphonio-2-hydroxybutyrate catalyzed by the MTHB methyltransferase enzyme (DYSB) (Curson et al., 2018), and finally undergoes oxidative decarboxylation to DMSP (**Figure 2**). DMSP can be degraded via two enzymatically-mediated pathways: a cleavage pathway that forms DMS, catalyzed by DMSP lyases (ddd), and a demethylation pathway that produces MeSH via series of enzymes including DMSP demethylase (dmdA) (Howard et al., 2006). MeSH can be converted to Met by *O*-acylhomoserine (Thiol)-lyases (metY1) (Ferla and Patrick, 2014). DMS is oxidized to DMSO by photochemical oxidation in the atmosphere and by microbial oxidation with monooxygenases in surface seawater; DMSO can be recycled back to DMS via a reduction pathway (Del Valle et al., 2009). DMSOP, derived from DMSP, is taken up and metabolized to DMSO by bacteria (Thume et al., 2018). MSA is one of the main products of DMS oxidation, generated via the reaction between $\cdot\text{OH}$ and NO_3^- radicals. Methanesulfonate monooxygenase (msmA) mediates the primary degradation of MSA to produce inorganic sulfite (Henriques and Marco, 2015).

Sulfonate Metabolisms

Sulfonation and desulfonation routes regulate the incorporation and release of sulfite via sub-pathways that generate a set of sulfonated compounds (**Figure 2**) (Cook et al., 1998). The biogenesis of SQDG involves the assembly of uridine 5'-diphospho (UDP)-SQ from UDP-glucose and sulfite by UDP-SQ synthase (sqdB) (Benning and Somerville, 1992b), and the glycosyltransferase-catalyzed conjugation of UDP-SQ to diacylglycerol by an acyltransferase (sqdA) (**Figure 2**).



(Benning and Somerville, 1992a). A sulfoquinovosidase (*yihQ*) identified in *Escherichia coli* catalyzes the hydrolysis of SQDG to SQ, which is the gateway enzyme for SQ degradation (Speciale et al., 2016). SQ has been shown to be degraded by certain aerobic as well as anaerobic bacteria (Roy et al., 2003; Denger et al., 2012, 2014; Felux et al., 2015; Burrichter et al., 2018) and two major sulfoglycolytic pathways, the sulfo-Embden-Meyerhof-Parnas pathway (originally found in *E. coli*) and the sulfo-Entner-Doudoroff pathway (originally found in *Pseudomonas putida* SQ1) have been described (Denger et al., 2014; Felux et al., 2015). These pathways are analogous to the classic glycolysis pathways (Figure 2) (Felux et al., 2015). Bacterial SQ degradation yields the C3-organosulfonate products DHPS and sulfolactate (Figure 2)

(Roy et al., 2003; Denger et al., 2012, 2014; Felux et al., 2015; Burrichter et al., 2018). These products can be excreted for further bacterial utilization.

The DHPS degradation pathway in aerobic bacteria involves a series of hydrogenase enzymes (*hpsO*, *hpsP*, and *hpsN*) that produce sulfolactate (Figure 2) (Mayer et al., 2010). Sulfolactate is metabolized by bacteria via three enzymatic pathways (Figure 2) (Graupner et al., 2000; Denger et al., 2009; Mayer et al., 2010). The first pathway converts sulfolactate into pyruvate and sulfite using sulfolactate sulfolyase (*suyAB*) (Figure 2). The second pathway oxidizes sulfolactate to sulfopyruvate using sulfolactate dehydrogenase (*comC* or *slcC*) (Mayer et al., 2010), transaminates sulfopyruvate to L-cysteate, and desulfonates

L-cysteate using L-cysteate sulfo-lyase (*cuyA*) to produce pyruvate and sulfite (Figure 2) (Denger et al., 2009). The third pathway decarboxylates sulfopyruvate to sulfoacetaldehyde using sulfopyruvate decarboxylase (*comD* and *comE*), and then desulfonates sulfoacetaldehyde using sulfoacetaldehyde acetyltransferase (*xsc*) to yield acetyl-CoA and sulfite (Figure 2) (Graupner et al., 2000). The produced sulfite may either be exported by a specific exporter, or act as a source for other sulfur metabolites (Durham et al., 2015). DHPS also can be degraded completely by *Desulfovibrio* sp. DF1 under anaerobic conditions, yielding acetate and sulfide (Burrichter et al., 2018).

Taurine can be derived from Cys via the activities of Cys dioxygenase and Cys sulfenic acid decarboxylase in phytoplankton cells (Tevatia et al., 2015). Alternatively, taurine may be produced from cysteate via a decarboxylation step (Agnello et al., 2013). Taurine can then be degraded by taurine dioxygenase (*tauD*) into either aminoacetaldehyde plus sulfite or sulfoacetaldehyde (Figure 2) (Van der Ploeg et al., 1996).

Sulfate Esters Metabolisms

PAPS is an important sulfuryl donor for various metabolites via specific sulfotransferases (Figure 2); for example, PAPS may donate sulfur for the grafting of a sulfate ester onto aliphatic compounds (e.g., choline sulfate) or carbohydrates (e.g., heparan sulfate and chondroitin sulfate) (Chapman et al., 2004). Sulfate esters provide bacteria with either sulfur or carbon source, and microorganisms have genes encoding sulfatase enzymes that catalyze the hydrolysis of sulfates from various sulfate esters. The choline-sulfatase (*betC*) catalyzes the hydrolysis of choline sulfate to choline (Østerås et al., 1998), while *N*-acetylglucosamine-6-sulfatase (GNS) and *N*-acetylgalactosamine-6-sulfatase (GALNS) catalyze the hydrolysis of ester-bonded sulfur from heparan sulfate and chondroitin sulfate, respectively (Helbert, 2017).

GENES FOR THE INTERCONVERSION BETWEEN ORGANIC AND INORGANIC SULFUR IN THE OCEAN

In the sulfur metabolic network (Figure 2), thiols (e.g., Cys, GSH, L-homocysteine, and MeSH), sulfate esters (e.g., APS), and sulfonated compounds (e.g., taurine, cysteate, SL, sulfoacetadehyde, and MSA) are directly desulfurized to produce inorganic sulfur (Figure 2). These compounds are thus key intermediates in the recycling and mineralization of organosulfur to form inorganic sulfur species. Of these compounds, Cys, L-homocysteine, MeSH and 3-mercaptoproprylate may be sources of sulfide, and the desulfonation of sulfoacetadehyde, sulfolactate, taurine and MSA releases sulfite (Figure 3), catalyzed predominantly by microbial enzymes. The corresponding genes were distributed among a variety of divergent bacterial taxa (Figure 3 and Supplementary Datasheet S1). The frequency of these sulfur metabolism genes in the *Tara Oceans* database provided a rough estimate of the prevalence of genes in ocean waters, ranging from a low of approximately 2 per million sequences for *mstA* (encoding methylthiol: coenzyme

M methyltransferase) to high of approximately 31 per million sequences for *cysK/cysM* (encoding cysteine synthase) (Figure 3).

Cys as a Sink of Sulfate

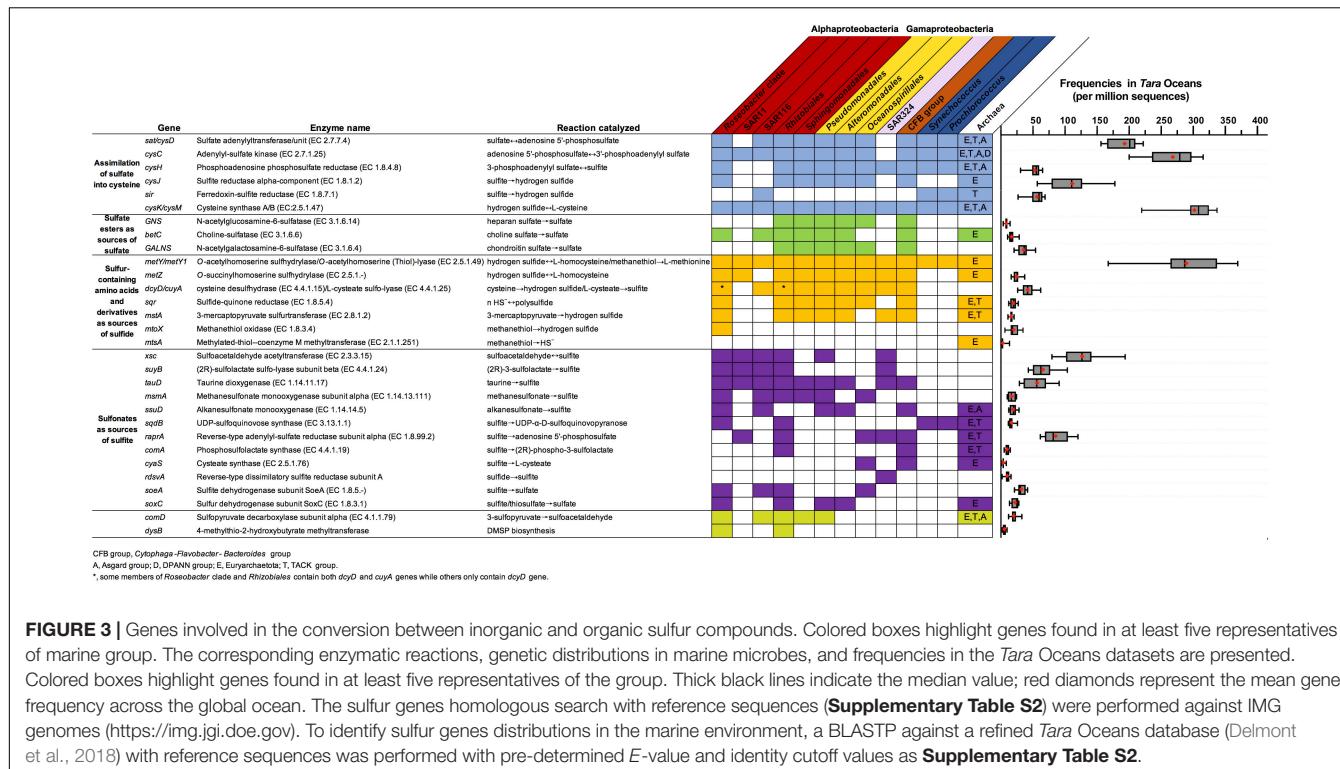
A genetic basis for sulfate assimilation has been identified in diverse bacterial and archeal taxa, including Proteobacteria, Cyanobacteria, Bacteroides, and Archaea (Figure 3). Taxa in the SAR11 clade, which are important for organic sulfur turnover, make up 33% of all euphotic-zone bacteria and 25% of all mesopelagic bacteria (Giovannoni, 2017). Genes encoding the *cysC* and *cysM* proteins in the sulfate assimilation pathway have been identified in all available SAR11 genomes (Tripp et al., 2008). However, other essential genes for assimilation of sulfur into Cys are lacking in SAR11, including *sat/cysD*, *cysH* and *cysJ/sir* (encoding sulfite reductase) (Figure 3), and hence they require exogenous sources of reduced sulfur to support their growth (Tripp et al., 2008). In contrast to the Euryarchaeota and the TACK, the Asgard and DPANN superphyla of the Archaea lack sulfate assimilation abilities (Figure 3).

Sulfate Esters as Sources of Sulfate

The average frequencies of three sulfatases genes (*betC*, GNS and GALNS) are low in the global ocean (Figure 3). Although SAR11, SAR324, and cyanobacteria lack sulfatase genes (Figure 3), *betC* genes have been identified in the *Roseobacter*, SAR116, and Euryarchaeota (Figure 3). Members of the *Cytophaga-Flavobacteria-Bacteroides* (CFB) group have an unusually high number of sulfatase-encoding genes, which are associated with the degradation of sulfated marine algal polysaccharides; these genes may be upregulated in CFB taxa when concentrations of sulfated organics increase significantly (e.g., during the phytoplankton blooms) (Teeling et al., 2016).

Sulfur-Containing Amino Acids and Derivatives as Sources of Sulfide

The absence of *aprAB* and *dsrAB* genes in the dissimilatory sulfate reduction pathway in *Tara Oceans* datasets shows that the reduction of sulfate to sulfide occurs rarely in the seawaters; in contrast, Cys and its derivatives are regarded as potential sources of sulfide (Figure 3). Genes *metY* and *metZ* (encoding O-succinylhomoserine sulfhydrylase) have been identified in most bacteria and Euryarchaeota (Figure 3), suggesting that these taxa have the capacity to use homocysteine as sulfide sources (Figure 3). In bacteria, Cys desulphydrase (*dycD*) and 3-mercaptoproprylate sulfurtransferase (*mstA*) are believed to be chiefly responsible for sulfide biogenesis from Cys and 3-mercaptoproprylate (Carbonero et al., 2012), respectively. However, the corresponding genes have not been identified in SAR11 or cyanobacterial genomes. The microbial catabolism of MeSH releases sulfide through the enzymatic activity of methanethiol oxidase (*mtoX*) (Eyice et al., 2018) or *mtsA* (Carrión et al., 2017). The *mtoX* genes are widely distributed in marine environments and are more abundant than *mstA* genes (Figure 3). The *mtoX* gene is found not only in methylotrophic bacteria (Carrión et al., 2019) but also taxa in the *Roseobacter* clade, including *Ruegeria pomeroyi* DSS-3, a DMSP-degrading



bacterium (Eyice et al., 2018). This suggests a possible pathway for sulfide production from DMSP in the marine environment. Some *Oceanospirillales* and *Euryarchaeota* genomes harbor the *mstA* gene (Figure 3). Sulfide:quinone oxidoreductase (sqr), which is an important enzyme for microbial sulfide oxidation (Friedrich et al., 2001), is absent in major bacterial taxa in marine environments (e.g., SAR11 and cyanobacteria) (Figure 3).

Sulfonates as Sources and Sinks of Sulfite

Besides sulfite from assimilatory sulfate reduction pathway, sulfonates were the main sources of endogenous production of sulfite in microbes. Several genes associated with the desulfonation of sulfoacetadehyde (*xsc*), sulfolactate (*suyB*), taurine (*tauD*) are highly abundant in the *Tara Oceans* datasets (Figure 3). This suggests that many marine microbes have the potential to degrade sulfonate. For example, such genes are present in Alphaproteobacteria (mainly in the order *Rhizobiales*, the genus *Roseobacter*, and the clades SAR11 and SAR116), but are absent in the cyanobacteria and archaea (Figure 3). The gene *tauD* was also identified in the bacterial orders *Pseudomonadales*, *Alteromonadales*, *Oceanospirillales* (in the Gammaproteobacteria; Figure 3). Members of the ubiquitous alphaproteobacterial SAR11 clade account for a large fraction of the cells that take up taurine, especially in surface waters (Clifford et al., 2019). Genes important for the desulfonation of cysteate (*cuyA*), methanesulfonate (*msmA*) and alkane sulfonate (*ssuD*) have been identified in *Roseobacter* species, and may allow these bacteria to use a broad range of sulfonates for growth (Figure 3).

Members of the SAR116 and *Pseudomonadales* clades harbored the genes *msmA* and *ssuD* (Figure 3). The *rdsVA* gene, which was identified in SAR324 (Figure 3), codes for a reverse operating siroheme dissimilatory sulfite reductase subunit that catalyzes the direct oxidation of sulfide into sulfite (Swan et al., 2011).

The involvement of *sqdB* in SQDG biosynthesis is not ubiquitous across the heterotrophic bacteria, with the exception of the *Roseobacter* clade and the order *Rhizobiales* (Figure 3). Members of the cyanobacteria and archaea harbor *sqdB* genes (Figure 3). Most of the *sqdB* genes known to be involved in SQDG synthesis identified in the surface waters of the Sargasso Sea and the North Sea were affiliated with cyanobacteria, not heterotrophic bacteria (Van Mooy et al., 2006; Villanueva et al., 2014). The gene *soeA*, encoding a subunit of the sulfite-oxidizing enzyme, is found in the *Roseobacter* clade; this gene is involved in sulfite oxidation (Boughammi et al., 2016). The gene *soxC*, from the *sox* system, is implicated in sulfite oxidation and is frequently identified in sulfur-oxidizing bacteria (Kappler and Dahl, 2001). Another sulfite oxidation reaction is mediated by cytoplasmic reverse APS reductase (encoded by *raprA* and *raprB*); in SAR11, cytoplasmic reverse APS reductase may utilize AMP and sulfite to generate APS (Kappler and Dahl, 2001), as a mechanism for the intracellular detoxification of sulfite (Meyer et al., 2007). The *raprA* gene was common in the *Tara Oceans* datasets, indicating that the potential for sulfite oxidation is ubiquitous in seawater (Figure 3). It has been proposed that dissimilatory sulfur oxidation may be used for the energetic support of carbon fixation in autotrophic SAR324 populations based on the presence of both *raprA* and *rdsVA* genes (Swan et al., 2011). Phosphosulfolactate synthase (*comA*)

and cysteate synthase (*cyaS*) in some archaeal methanogens incorporate sulfite into phosphoenolpyruvate and phosphoserine to form phosphosulfolactate and cysteate, respectively (Graham et al., 2002, 2009).

GENOMIC INSIGHT INTO DMSP AND DHPS TRANSFORMATION IN THE OCEAN

Genes involved in DMSP and DHPS transformation play crucial roles in the sulfur cycling of the oceans (Howard et al., 2006; Durham et al., 2019). The key intermediates MTHB and the *dysB* enzyme were identified in the marine bacteria *Labrenzia aggregata* LZB033, indicating that DMSP biosynthesis via Met transamination may operate in heterotrophic bacteria (Curson et al., 2017). Only 140 sequences homologous to *dysB* were identified in the Alphaproteobacteria genomes, and the frequency of the *dysB* gene was low in the *Tara Oceans* datasets, indicating that heterotrophic bacteria were not major DMSP producers in the surface ocean, as compared to the large phytoplankton. Seven distinct functional DMSP lyase genes (*dddD*, *dddK*, *dddL*, *dddP*, *dddQ*, *dddY*, and *dddW*) are found in the proteobacteria (Todd et al., 2009, 2010, 2011; Curson et al., 2011a,b; Sun et al., 2016). An additional functional DMSP lyase gene, *Alma1*, is firstly annotated and the most highly expressed in the alga *Emiliania huxleyi* (Alcolombri et al., 2015). The *dddK* genes are the most abundant bacterial DMSP lyase genes found in the marine metagenome (Landa et al., 2019). The *ddd* genes have been identified in the marine Alphaproteobacteria (e.g., the *Roseobacter* clade, SAR11, and SAR116), as well as in the Gammaproteobacteria (Moran et al., 2012; Sun et al., 2016; Nowinski et al., 2019). Homologs of the DMSP demethylase gene *dmdA* appeared to be more abundant in marine environments than the DMSP lyase genes or the DHPS utilization gene *hpsN* (Figure 4). The genes *dmdA* and *hpsN* are known to be harbored by the members of the *Roseobacter*, SAR11, SAR116, SAR324, and Gammaproteobacteria. SAR11 and *Roseobacter* carry most of the *dmdA* and *hpsN* genes identified in the euphotic zones, whereas SAR324 and Gammaproteobacteria carry the majority of the *hpsN* genes identified in the mesopelagic zones (Landa et al., 2019). The relative global abundance of *dmdA*, *ddd*, and *hpsN* in the *Tara Oceans* datasets was 0.09–0.65 genes cell⁻¹ (30–300 per million reads), 0.05–0.51 genes cell⁻¹ (18–160 per million reads), and 0.01–0.50 genes cell⁻¹ (25–210 per million reads), respectively (Figure 4). These genes are ubiquitous in the global euphotic and mesopelagic zones (Figure 4). Surface water and water at the depth of the deep chlorophyll maximum had significantly higher relative abundances of these three genes than water in the mesopelagic zones ($p < 0.05$, Figure 4). The highest average relative abundances of *dmdA* and *hpsN* (genes per cell) in the eutrophic zones were observed in the Mediterranean Sea, and the lowest abundances were observed in the Southern Ocean (Figure 4). However, abundances were highly variable in each oceanic region.

FUTURE PERSPECTIVES

The annual production of DMSP, which is well studied, accounts for approximately 18% of yearly sulfur assimilation by marine primary producers (Curson et al., 2017). However, other relevant compounds in the sulfur cycle are far less studied, leaving many questions regarding the biochemistry of sulfur metabolites unanswered. Furthermore, the relative importance of the processes affecting organic sulfur dynamics, especially in the deep ocean and sediments, are relatively poorly constrained. Recent studies of sulfonates, which have combined ‘omic’ and chemical detection methods, deserve careful attention as there is a crucial link between marine heterotrophic bacteria and primary producers (Durham et al., 2019; Landa et al., 2019). Here, current research is synthesized, gaps in our understanding of organic sulfur are highlighted, and future research directions are recommended.

Characterizations of Substrates and Specific Enzymes

Details of the chemistry and biochemical machinery of organic sulfur transformation can help us to untangle intriguing and hitherto unresolved sulfur biogeochemical processes. Despite the successful detection of cellular sulfur metabolites and DOS in seawater using mass spectrometry-based techniques, such as Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR-MS), these compounds remain largely undefined at barely detectable levels. However, DOS extraction methods, such as solid phase extraction, are likely to remove many small polar compounds prior to mass spectrometry analyses; for example, solid phase extraction may remove dissolved DHPS with an extraction efficiency of ~1% (Johnson et al., 2017). The quantification of sulfonates in seawater, including SQ, SQDG, and DHPS, is an important challenge for sulfur chemical ecology. Genomic data for reactions enzymatically catalyzed by organic sulfur in eukaryotic phytoplankton are severely limited. Recently proposed sulfonate metabolic pathways showed that the sulfur in DHPS might originally arise from Cys and PAPS, or might be directly derived from the sulfonation of glycerol phosphate (Durham et al., 2019). This helps to explain the high levels of DHPS inside phytoplankton cells. However, the enzymes that catalyze DHPS synthesis are still unknown. All cyanobacteria were believed to lack *dmdA* gene (González et al., 2019), however, they can take up and assimilate DMSP via an as-yet-unidentified pathway (Malmstrom et al., 2005). In addition, the enzymatic or chemical mechanisms of DMSOP synthesis in DMSP and DMS cycling remained unclear (Thume et al., 2018). The microbial uptake of exogenous sulfur-containing compounds, such as Cys, Met, GSH, DHPS, DMSP and taurine, requires transporter proteins (Supplementary Table S3), but specific transporters for many known sulfur metabolites still await discovery. Enantioselective and diastereoselective interactions may occur between chiral sulfonates and enzymes. For example, the enzymes *hpsN* and *hspO* may act on R-DHPS and S-DHPS, respectively, but experimental evidence for these interactions are lacking. Although the molecular configuration of DHPS

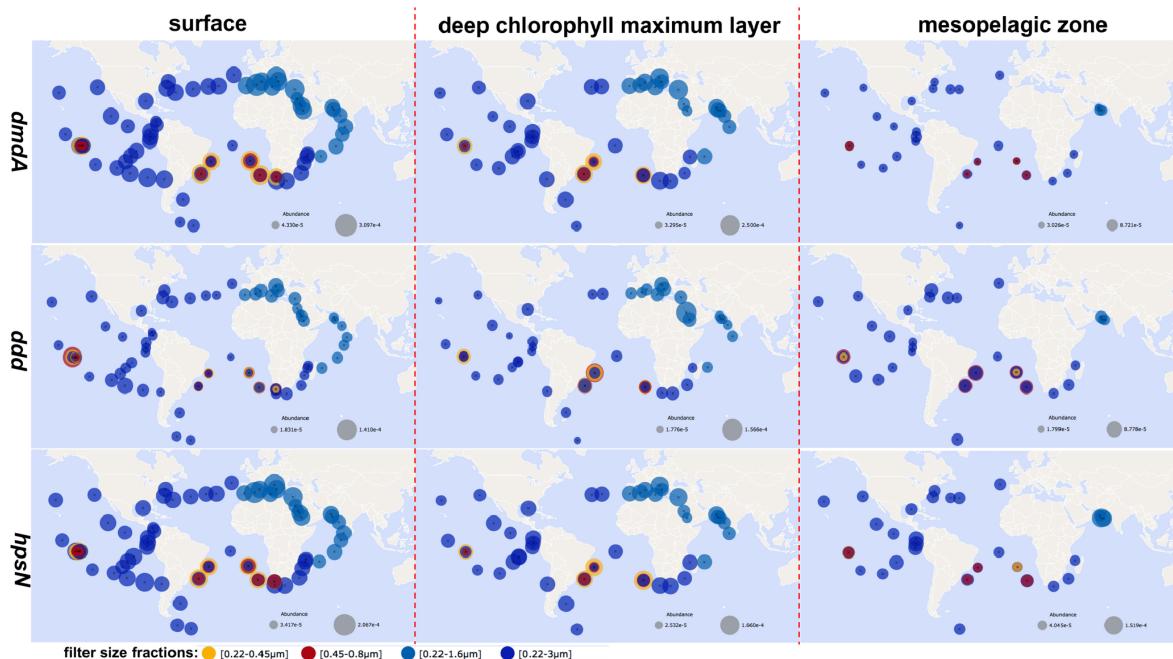


FIGURE 4 | Biogeography of *dmdA*, *ddd*, and *hpsN*. The relative abundances of these genes at each station (gene sequences/total sequences) were derived from the Ocean Gene Atlas across the different size fractions and sampling depths (<http://tara-oceans.mio.osupytheas.fr/ocean-gene-atlas/>) (Villar et al., 2018) using reference sequences via BLASTP (*E*-value: *dmdA* (Q4FP21) 1×10^{-20} ; *ddd* (Q5LSR3) 1×10^{-20} ; *hpsN* (Q5LVV1) 1×10^{-40}).

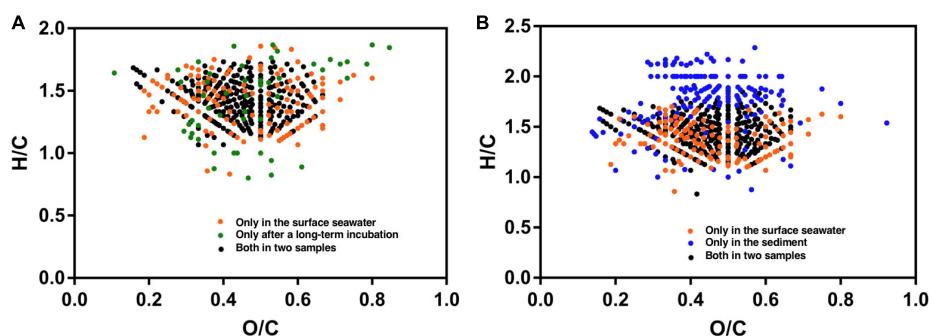


FIGURE 5 | Van Krevelen diagrams [hydrogen-to-carbon (H/C) and oxygen-to-carbon (O/C) ratios] showing the S-containing formulae derived from FT-ICR-MS (data derived from Cai et al., 2019). **(A)** Samples from the surface water and incubation experiments using surface water (110 days at 20°C). **(B)** Samples from the surface water and surficial sediment.

in natural environments is unknown, SAR11 seems to only utilize one enantiomeric form of DHPS as SAR11 taxa possesses only the *hpsN* gene. In contrast, *Roseobacter* species metabolize two enantiomeric forms of DHPS and possess both *hpsN* and *hpsO*. Thus, the future discovery and characterization of novel substrates and enzymes is essential for a better understanding of a key step in the sulfur cycle.

Revealing Organosulfur Cycling in the Dark Ocean and Sediment

Although the pelagic realm of the dark ocean is the largest reservoir of heterogeneous DOS in the ocean (>6,700 Tg S), few

details are known about the source and sink of biogenic sulfur in this region (Ksionzek et al., 2016). Deep-ocean DOS is thought mainly to originate from biological processes in the upper ocean and from organic matter transported from the upper ocean to the deep ocean and sediments; DOS in the deep ocean may persist for thousands of years (Koch et al., 2017). The most important biologically mediated processes regulating the long term storage of organic matter in the ocean are the biological carbon pump (Ducklow et al., 2001) and the microbial carbon pump (Jiao et al., 2010, 2014, 2018). After the long-term incubation (110 days) of a microbial community in natural seawater, more sulfur metabolites may be produced, suggesting that biotic process lead to the formation of refractory compounds (Figure 5A)

(Cai et al., 2019). SQDG is efficiently removed as it sinks to the deep sea; in contrast, around 40 sulfur-containing lipids, likely produced by photoautotrophs in the upper ocean, are potentially important as deep-ocean carbon storage compounds (Schubotz et al., 2018). However, the hundreds of DOS identified in the deep sea far exceeds the number of DOS substrates taken up by microbial transporters (**Supplementary Table S3**). In addition, although the affinity of transporter constants (K_s) varies greatly from millimolar to nanomolar, this affinity is generally higher than the apparent picomolar concentrations of DOS. Thus, DOS in the deep ocean is either intrinsically refractory or present in extremely low concentrations, resulting in its resistance to microbial utilization. Besides describing the molecular composition of deep-sea DOS, future work should investigate whether the microbial carbon pump combined with biological pump carbon transforms organic sulfur into refractory one. If so, this might help explain the observed huge DOS pool in the dark ocean.

Organic sulfur is the second most important reduced sulfur pool in sedimentary environments. FT-ICR-MS has shown that organic sulfur in surficial sediments is composed of a heterogeneous mixture of sulfur compounds (Cai et al., 2019). These compounds are considerably different from sulfur compounds identified in seawater. For example, unique saturated compounds with relatively high hydrogen to carbon ratios have been identified in sediment (**Figure 5B**). Bacteria have recently been shown to be an important source of DMSP; high concentrations of DMSP are produced by certain bacterial species (Williams et al., 2019). Moreover, MeSH and DMS consumption processes, mediated by bacteria, were observed in the surficial sediments of a coastal saltmarsh (Williams et al., 2019). Although sulfonated organics generally account for 20–40% of all organic sulfur in marine sediments (Vairavamurthy et al., 1994), their sources and fates remain unclear. Both biotic and abiotic processes of organic matter diagenetic sulfurization may occur in the sulfidic sediments (Pohluelke et al., 2017), whereby sulfate-reducing microorganisms might substantially contribute to sulfide incorporation into organic matter through the dissimilatory sulfur reduction pathway. Such diagenetically formed organic sulfur compounds might be buried during carbon sequestration as they may not be recognized by microbial enzymes (Wasmund et al., 2017). Future studies of the biogeochemical processes of sedimentary organic sulfur might substantially expand our understanding of the marine sulfur cycle.

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SUMMARY

Biogenic organic sulfur compounds have diverse chemical forms and play essential biological roles in marine organisms. Methyl-sulfur compounds, sulfonates, thiols, sulfolipids, and sulfate esters are widespread and represent a significant fraction of the DOS pool in the upper ocean. Phytoplankton, which produce much labile organic sulfur, together with heterotrophic bacteria, plays a major role in the carbon and sulfur fluxes in the pelagic ocean via a large set of sulfur metabolites that are intertwined in the biochemical reaction network. Methylated sulfur compounds and sulfonate catabolisms allow the microbial acquisition of reduced sulfur and carbon from organic sulfur compounds. Taxa in the *Roseobacter*, SAR11, SAR116, SAR324, and Gammaproteobacteria constitute an important gene pool for the transformation and mineralization of organic sulfur in the upper ocean. Future research on the characterization of novel substrates and enzymes involved in sulfur metabolism, and the investigation of organic sulfur transformation in the deep sea and in sediments, are essential steps toward a comprehensive understanding of the microbial contribution to the marine sulfur cycle.

AUTHOR CONTRIBUTIONS

KT conceived of and wrote the manuscript.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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