REVIEW ARTICLE
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Microbial metabolites in the marine carbon cycle

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One-quarter of photosynthesis-derived carbon on Earth rapidly cycles through a set of short-lived seawater metabolites that are generated from the activities of marine phytoplankton, bacteria, grazers and viruses. Here we discuss the sources of microbial metabolites in the surface ocean, their roles in ecology and biogeochemistry, and approaches that can be used to analyse them from chemistry, biology, modelling and data science. Although microbial-derived metabolites account for only a minor fraction of the total reservoir of marine dissolved organic carbon, their flux and fate underpins the central role of the ocean in sustaining life on Earth.

Organic molecules dissolved in seawater are cycled through the sunlit ocean by the billion marine microbes living in each litre of surface water[1] (Fig. 1). This process involves almost half of the annual net primary production (NPP) of the ocean; therefore, even minor changes in its output lead to important effects on a global scale. Much remains unknown about the chemicals passing through the labile dissolved organic carbon (DOC) pool, largely because they are highly bioavailable and they are almost simultaneously produced and consumed by diverse marine microbes. Specifically, the surface ocean labile DOC pool has a turnover of about three days[2], with steady-state concentrations in the range of nanomolar to picomolar[3,4] for compounds abundant enough to be measured with existing methods and below this range for many others.

This low abundance of microbial metabolites in seawater presents a conundrum, as compounds supporting one of the most important fluxes in the carbon cycle of Earth are among the most challenging to study. In this Review, we summarize our current understanding of the sources and fate of marine microbial metabolites in the surface ocean and describe current and emerging analytical approaches for learning about their roles.

Marine sources of labile DOC

Most labile DOC of marine origin is produced by one of three sources: actively photosynthesizing phytoplankton, senescing and dead phytoplankton, or heterotrophic organisms.

Actively photosynthesizing marine phytoplankton generate exometabolites (metabolites released into surrounding seawater) that form a pool of carbon named 'extracellular release'[5] or 'dissolved primary production'[6] (Fig. 2). These released compounds are resources that are now lost from phytoplankton cells, and different hypotheses for the mechanisms underlying their release have been proposed[7]. For example, the million-fold concentration differential between the inside and outside of phytoplankton cell membranes[8] could drive a molecular diffusion process by which healthy cells continually leak a fraction of their internal metabolites into seawater[9]. Leakage would be a passive process, and low-molecular-weight (<600 Da) and hydrophobic compounds (due to cell membrane composition) are more likely to leak out[7,9,10]. In active mechanisms of extracellular release, labile DOC would be excreted rather than lost from living phytoplankton, which enables control over the rates and composition of the released metabolites. Physiological stresses imposed by photosynthesis are likely to drive active carbon export, and several mechanisms related to stress have been proposed. For example, when carbon dioxide (CO_2) is limiting, the principal carbon-fixation enzyme binds oxygen instead, which results in the production and release of toxic photorespiration products[11] such as glycolate[12]. Conversely, when nutrients are limiting but inorganic carbon and irradiance are not, carbon fixation can outpace macromolecule synthesis[13] and cause extracellular release of the excess fixed carbon in the form of polysaccharides and organic acids, which are referred to as 'photosynthetic

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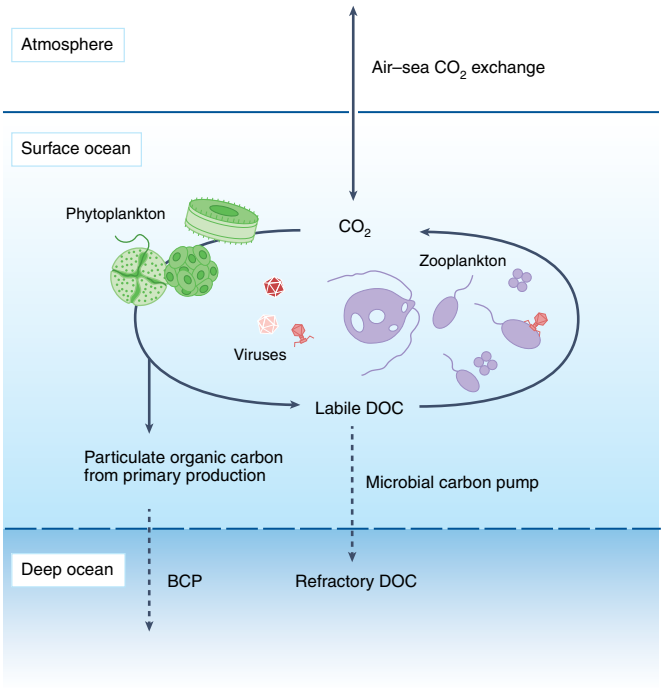


Fig. 1 | Microbial metabolites drive the carbon cycle in the surface ocean. Metabolites in the labile DOC are synthesized by phytoplankton and other microbes and released into seawater through exudation, leakage, sloppy feeding and lysis. Within hours to days, they are consumed primarily by heterotrophic bacteria for growth and energy. The respiration of labile DOC adds CO_2 back to the surface ocean, which influences air–sea exchange. A small fraction of labile DOC is converted to non-labile forms and participates in long-term carbon storage in the deep ocean (microbial carbon pump). Fixed carbon that is not processed as labile DOC includes living microbes and metazoa, particulate detritus and refractory DOC, with a fraction transported to the deep ocean via the biological carbon pump (BCP).

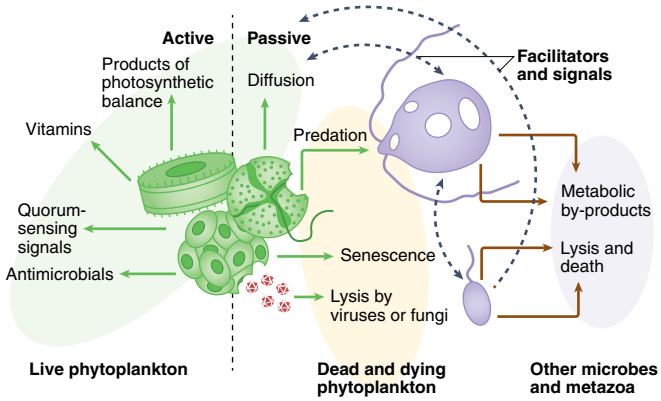


Fig. 2 | Sources of the labile microbial metabolites in the surface ocean. Green arrows indicate substrate metabolites derived from primary production, whereas brown arrows indicate those from secondary production. The contributions of the three main sources can only be hypothesized at this time[60] (see the main text) given large reported ranges in the per cent of primary production released in dissolved form[5,228], biases from measurement artefacts (for example, cell disruption during filtration[5] or differential radiolabelling of microbial intracellular pools[19]) and influences of environmental factors such as photosynthetic rate[19,228], irradiance levels, nutrient limitations, bloom stage and temperature[32]. Dotted arrows indicate facilitator and ecological signal metabolites that can indirectly contribute to carbon flux through influences on microbial activity.

overflow'[13–16]. Nutrient stress has also been proposed to drive organic carbon excretion as a by-product of cells increasing their ATP/ADP ratio (that is, reaching a higher intracellular energy state) to mitigate the free-energy costs of transport of low concentration nutrients[17]. These nutrient-limitation-driven mechanisms should favour the excretion of carbon-rich compounds[17]. At points in the diel cycle and regions in the photic zone where light shock can occur, extracellular release from phytoplankton may occur in response to a redox imbalance[18,19]. Finally, phytoplankton actively release molecules that trigger behavioural or physiological changes in neighbouring microbes. These metabolites often have distinctive chemical structures and can function as defence compounds[20], pheromones[21] or toxins[22,23]. Given the different mechanisms and drivers of release, the chemical composition of phytoplankton exometabolites should differ from the composition of endometabolites (those present in the cell). This has indeed been observed for amino acids, carbohydrates and carboxylic acids[24–26]. Regardless of the release mechanism, the tight coordination in daily activity patterns between phytoplankton and heterotrophic bacteria that track the diel irradiance cycle[18,27,28] establishes a major role for extracellular products of photosynthetic activity in carbon transfer in the surface ocean (Fig. 3).

Phytoplankton senescence and death liberate endometabolites that form a second large source of labile molecules[29,30] (Fig. 2). For example, sloppy feeding (escape of organic matter during grazing) or egestion (release of organic matter remaining undigested in guts and food vacuoles of predators)[31–33] is carried out by protist and zooplankton predators and results in the release of dissolved organic matter from phytoplankton prey, which liberates 10–30% of prey carbon. Viral lysis of phytoplankton cells releases various metabolites[34,35], the composition of which depends on host reprogramming during infection[36,37]. Recent evidence suggests that microparasitic fungi also change the intracellular chemistry of their host, similarly modifying the composition of released metabolites[38]. Senescence or 'autocatalytic cell death' triggered by nutrient limitation or other stresses is also a source of metabolites[10,29] and may be particularly important in declining blooms[39,40].

Finally, heterotrophs, including bacteria, archaea and protists, are the third main source of metabolic by-products generated by excretion or viral lysis[32,41–43] (Fig. 2; heterotrophic activities of mixotrophic protists are counted here[44]). Viral infection can modify bacterial endometabolomes[45] through reprogramming of host metabolism[45,46], which is an important component of labile DOC given estimates that one in three ocean bacteria are infected at any time[34]. Organic molecules originating from heterotrophic protists and zooplankton can be rich in organic nitrogen[47] and are readily scavenged by bacteria[33]. Heterotrophic marine bacteria and archaea release thousands of different molecules[48–51] that might serve as bacterial substrates[52]. Liberation of labile compounds also occurs during bacterial solubilization of polymeric components of particulate detritus[53], such as proteins and polysaccharides, whose degradation products diffuse from the particle surface[54–57].

Fraction of carbon routed through microbial metabolites

Each year, heterotrophic marine bacteria are predicted to process ~20 PgC from the labile DOC pool (Fig. 1), as estimated by both geochemical methods based on DOC reactivity[2] and ecological approaches based on bacterial carbon demand[58] (that is, bacterial secondary production plus respiration). This routing of recently fixed carbon to bacteria through labile DOC is one of the largest and most rapid fluxes of organic carbon in the biosphere. Two early estimates of marine carbon processed through the microbe–metabolite network were 10–50% (ref. [59]) and 40% (ref. [58]) of ocean NPP, and a recent compilation of bacterial carbon demand values is consistent

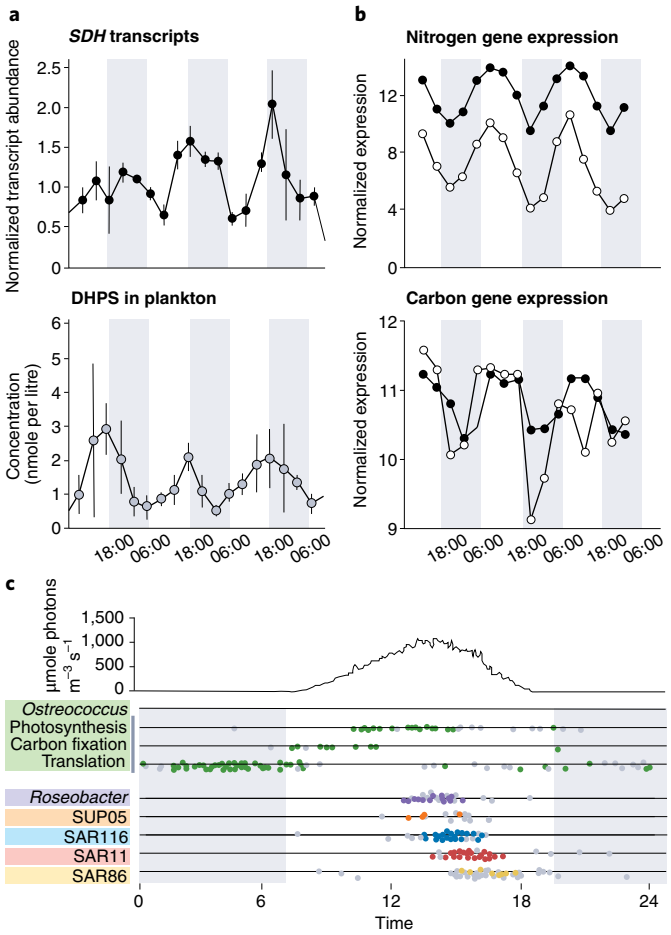


Fig. 3 | Diel synchrony in microbial synthesis, release and utilization of metabolites. a, Periodicity in expression of a diatom gene (*SDH*) in the DHPS biosynthetic pathway (top) is correlated with DHPS concentrations in phytoplankton metabolomes (bottom) in surface waters of the North Pacific Subtropical Gyre. Expression data are transcripts per litre, normalized to the mean. Error bars represent the standard deviation ($n = 3$). Data are from ref. [18]. **b**, Periodicity in relative gene expression by *Trichodesmium* (filled symbols) is correlated with expression by its associated microbiome (open symbols) for nitrogen fixation and metabolism genes (top) and carbon fixation and respiration genes (bottom) in the North Atlantic. Data are from ref. [173]. **c**, Gene expression patterns for key metabolic processes by dominant members of a coastal microbial community in California, averaged over six diel light cycles. Top: photosynthetically active radiation. Bottom: time of peak relative expression for individual genes. Coloured symbols represent genes with statistically significant diel patterns. Gene expression by the dominant primary producer (*Ostreococcus*, green symbols) is shown separately for (top to bottom) photosynthesis, carbon fixation and translation. Gene expression by five dominant heterotrophic bacterial groups is shown for translation. Grey shading represents night. Data are from ref. [27].

with these (52% of NPP[60]). Partitioning of inputs among the three major sources estimated from published values for labile DOC release by microbial and zooplankton activities suggested that ~40% of labile DOC originates directly from phytoplankton as extracellular release from photosynthesizing cells, ~40% is released from phytoplankton death processes (senescence, sloppy feeding, viral and fungal lysis) and ~20% is released from heterotroph excretion and death processes[60]. The magnitude of this last source is constrained by its derivation from secondary production, and therefore from organic carbon pools diminished by respiratory losses[61].

Molecular composition of labile DOC

The molecules that make up the labile DOC pool of the ocean have been highly challenging to identify. Early studies proposed that amino acids, carbohydrates, osmolytes and small carboxylic acids (in particular the photorespiration product glycolate) are the main substrates for surface ocean bacteria[1,14,62,63]. These compound classes were suggested by chemical analyses of plankton cells under the assumption that internal metabolite pools are proxies for released pools. Metabolites in intracellular pools are easier to measure than those in external pools because they typically have concentrations that are several orders of magnitude higher than in the surrounding seawater[63] (Table 1; micromolar to millimolar[14,64–67] internal versus picomolar to nanomolar[3,4,67] external). Furthermore, endometabolite samples can be concentrated by capturing cells on filters. However, paired analyses of endometabolites and exometabolites in phytoplankton cultures reveal that internal pools do not closely correspond to external pools[67], although viral lysis and sloppy feeding may be exceptions. This selective release of phytoplankton metabolites is not surprising but limits the accuracy of using endometabolomes to predict labile DOC composition. Nonetheless, endometabolite analyses of marine plankton have yielded candidates for the labile DOC inventory (Table 1). Examples include quaternary amines (for example, choline, dimethylglycine and trimethylamine-*N*-oxide), organic sulfur compounds (for example, gonyol, cysteate, dimethylsulfonioacetate and sulfolactate) and amino acid derivatives (for example, homarine, trigonelline and ornithine)[18,65,67–76] (Table 1).

Labile DOC components can be coarsely categorized on the basis of their physiological and ecological roles in the microbe–metabolite network of the ocean. Here we define three broad categories that capture several of these roles: substrates, facilitators and ecological signals (Box 1).

Substrate metabolites are defined as the compounds that are actively assimilated by marine bacteria for carbon and energy, and transferred among microbes in quantities that sustain growth, reproduction, and the cycles of carbon and other elements. Amino acids[77,78], polyamines[79,80], carbohydrates[81–83], sulfonate and sulfonium compounds[18,69], carboxylic acids[72,75,76,84], and nucleosides[70,72,75] all function as bacterial substrates in surface seawater (Table 1). Molecules in this category contribute most directly to flux by serving as the conduits or 'currencies' that move carbon among marine microbes.

Facilitator metabolites are defined as molecules that enable biochemical reactions and can be reused and exchanged among microbes (Box 1). Those that have been identified in seawater include the soluble B vitamins (B_1, B_7 and B_{12})[85–87], iron siderophores[88,89] and other biosynthesized metal-binding molecules[90,91], all of which have steady-state concentrations at the limit of bacterial uptake kinetics (<1 pM to tens of pM[92–95]), although concentrations can fluctuate in time and space. Both substrate and facilitator molecules are also considered 'public goods' if they are energetically expensive to synthesize and released by only a subset of the microbial community[96]; public goods can set the stage for metabolic dependencies within the microbial network of the ocean[97].

Ecological signal metabolites or 'infochemicals' are defined as compounds that orchestrate specialized microbial interactions under specific conditions[98,99]. Sourced and shared by microbes, they serve as the medium for interactions by altering community physiological or behavioural features through chemicals passed among members (Box 1). Microbially produced hormones, such as indole acetic acid[100], and quorum-sensing molecules, such as acyl homoserine lactones[101], are among the ecological signal compounds thus far discovered in ocean communities or cultivated marine microorganisms. Molecules that inhibit growth or cause mortality[42,75,102] are also categorized as ecological signal compounds in this Review because of their role in modifying physiology (albeit negatively) of

other microbes. Both facilitator and ecological signal metabolites can indirectly contribute to labile DOC cycling by affecting the rates and routes of carbon flux without constituting a substantial mass fraction themselves.

Challenges to understanding roles of labile DOC

Although expertise in marine metabolites is growing, we cannot yet unravel the roles of labile DOC molecules in carbon flux and fate in the surface ocean[103]. Roadblocks to progress can be boiled down to one (long) sentence: hidden among the hundreds of thousands of mostly unknown organic molecules embedded in a million-fold higher salt concentration are the currencies of a very large carbon flux through a very small carbon reservoir. Here, we pull apart this sentence and explain in more detail the specific challenges it captures.

Hidden in the highly complex marine DOC pool…. Each of the tremendous number of distinct microbial organisms that occupy surface seawater[104,105] can release tens to thousands of different molecules[48,49,51,67,106–109]. Genome-scale metabolic models based on flux balance analysis agree that microbial cells simultaneously maintain many hundreds of different endometabolites[110] that can potentially be lost or exported as labile DOC. Some of these are predicted to be 'costless' metabolites, such as by-products of anabolic and catabolic pathways released without any fitness costs to the microbe[111]. Untargeted mass spectrometry (MS) and nuclear magnetic resonance (NMR) analyses have indeed uncovered hundreds of thousands of distinct organic features in marine DOC[112,113], of which only 1–5% can be identified[114–116]. Manually intensive, low-throughput identification pipelines are currently the primary approach used to convert these unidentified compounds into chemical insight. Of course, the biological reactivities of all the unknown compounds are also unknown; therefore, biogeochemically important molecules cannot be singled out of this multitude. In short, we cannot identify which of these compounds are important substrates, facilitator metabolites or ecological signal metabolites, or are otherwise uninvolved in the labile DOC cycle.

…embedded in a salty matrix…. Salt is a frustrating problem for the analysis of marine DOC. In MS analysis, non-volatile salts interfere with ion formation and degrade spectral quality[117]. In NMR analysis, salts reduce probe sensitivity[118]. Accordingly, the development of methods to remove organic compounds from their salty matrix has been an essential endeavour in chemical oceanography. Strategies that have been explored include water and salt removal via tangential flow filtration (TFF)[119], reverse osmosis/electrodialysis[120] and metabolite capture on solid-phase extraction resins[121,122]. Yet only 10–40% of marine DOC is captured with these methods, with a bias towards moderate- (>300 Da) and high- (>1,000 Da) molecular-weight compounds. In particular, small and polar metabolites, which are characteristics of many labile biomolecules, are lost during TFF or reverse osmosis/electrodialysis and are not well retained on solid-phase extraction resins such as the styrene-divinylbenzene polymer PPL[122]. Other saline fluids that are more easily analysed for metabolite content have higher concentrations of molecules in a lower concentration of salt, for example, millimolar metabolite concentrations (up to million-fold higher than seawater) in 1–10 ppt salt solutions (up to 30-fold lower than seawater) characteristic of blood and urine. For now, the state-of-the-art techniques used to isolate organic molecules from seawater remain strongly biased against the low-molecular-weight and polar exometabolites[122], which form the majority of components of labile DOC.

…is a small metabolite reservoir with a very large flux. Labile DOC release is largely balanced over time by its consumption by heterotrophic bacteria, which maintain individual compounds in the picomolar-to-low-nanomolar concentration range[18,93,123–125] or lower. Specific uptake affinities for DOC components in oligotrophic marine bacteria are among the highest reported, for example, 150-fold higher than for well-studied model bacteria[93]. Oligotrophic bacteria (those that can survive on low organic matter concentrations) are so efficient at depleting the labile DOC pool that calculations suggest that they must simultaneously scavenge for at least 34 different substrates to grow at one generation per day[92]. Copiotrophic marine bacteria (those that require higher organic matter concentrations) have lower substrate affinities but higher maximum uptake rates that allow them to rapidly draw down local substrate spikes on the order of 100 nM to 1 µM (ref. [126]). It may be possible for a single bacterial taxon to switch between these life history strategies[127,128], but it is more probable that genetic makeup (for example, genome size, content and regulation) locks a heterotrophic bacterium into either a high- or low-affinity strategy[129–131]. Regardless of how affinity is apportioned among cells, the communities of marine bacteria in aggregate are capable of both high affinity and fast uptake to maintain low concentrations of labile DOC components in seawater, and are considerably better at detecting DOC than our state-of-the art chemical methods. Although targeted chemical methods have the sensitivity to directly measure some classes of metabolites in seawater, for example, amino acids[132], sugars[133] and organic sulfur molecules[69], untargeted methods that aim to maximize the number and novelty of detected molecules are challenged by the low natural concentrations[4].

The difficulty of characterizing the 'small reservoir' of labile DOC within the total DOC pool is intertwined with its 'large flux'. Cycling rates of metabolites are not predictable by their concentration in seawater and may even be inversely related[134]. For example, dimethylsulfoniopropionate (DMSP) has been estimated to support up to 10% of total bacterial carbon demand in the marine photic zone[135] yet has a steady-state concentration in the surface ocean of just ~3 nM (ref. [136]; Box 2). The most common method for estimating flux of recently fixed carbon into bacterial cells is to measure exudates released from ^{14}C-labelled phytoplankton cells in the absence of bacterial uptake[32], the so-called dissolved primary production. These estimates of carbon available for bacterial scavenging span a wide range (from 4% to 47% of NPP[15]) and provide no information on the specific compounds involved. Another approach captures the combined flux of labile DOC from all principal sources by determining the bacterial carbon demand as a percentage of ecosystem NPP. Results from this methodology suggest that ~40–60% of NPP is accessible to heterotrophs across a variety of marine environments, but with considerable uncertainties[58,60]. Moreover, these methods cannot directly observe carbon flux on the time scales (seconds to minutes) and space scales (micrometres) of many microbial processes[137–139].

Analytical methods for marine microbial metabolites

Chemical methodological advances. Although there are now more than 18,500 metabolites catalogued in the Kyoto Encyclopedia of Genes and Genomes (KEGG) compound database[140], an untold number, including many with central roles in biogeochemical cycling, are still missing. A strategic approach is needed to focus on those currencies most relevant in driving the carbon cycle of the ocean. Molecular-level characterization of marine DOC has been a goal for decades in chemical oceanography and organic geochemistry, but has been thwarted by the salt and concentration challenges detailed above as well as by instrument limitations. Metabolite identification has emerged as a substantial bottleneck because the complex mixtures contain numerous isobaric and isomeric compounds that are poorly represented in current reference databases that are biased towards human metabolites and human-associated metabolites. Advances in both MS and NMR have now begun to crack this DOC black box (Fig. 4). The advent of electrospray

Table 1 | Marine microbial metabolites

Metabolite	Exometabolite in seawater	Exometabolite in culture	Endometabolite in marine plankton	Endometabolite in culture	Refs.
1-Methylhistidine		×			75
2′-Deoxyguanosine		×			4
2,3-Dihydroxybenzoate	×				108
3-Dehydroshikimate		×			225
3-Hydroxybutyrate				×	76
3-Mercaptopropionate	×	×			67,108
3-Phosphoglycerate		×			75
4-Acetamidobutanoate		×			75
4-Amino-5-aminomethyl-2-methylpyrimidine					3
4-Amino-5-hydroxymethyl-2-methylpyrimidine	×	×			4
4-Aminobenzoate	×	×			3,108
4-Aminobutanoate		×			75
4-Hydroxybenzaldehyde		×			75
4-Hydroxybenzoate	×	×	×		3,67,108,116
4-Hydroxyphenylacetate		×		×	75,76
4-Hydroxyphenylglycine		×			75
5′-Methylthioadenosine		×	×	×	3,116,225
5′-Uridine monophosphate	×	×			4,108
6-Phosphogluconate	×				108
(6*R*)-5,6,7,8-Tetrahydrobiopterin		×			4
7-Dehydrocholesterol			×		64
α-Aminoadipate		×			75
α-Ketoglutarate	×				3
α-Ribazole		×			225
β-1,3-Glucan				×	76
Acetate				×	76
Acetyltaurine	×				3
Aconitate			×		64
Adenine	×	×			3,4,64
Adenosine	×	×	×	×	3,4,64,67,70,75,108,116
Adenosine monophosphate			×		4,64,67,70,116
Aminobutyrate			×		64
Alanine	×	×	×	×	4,64,65,76
Arachidonate			×		64
Arginine	×	×	×	×	3,4,64,65,67,70,76,116
Asparagine	×	×	×	×	4,64,76
Aspartate	×	×	×	×	64,65,76
Azelaiate		×			75
Biotin	×		×		108,116
C_{16}-hydroxy-glycerophosphocholine		×			75
Caffeine	×		×		3,64,116
Carnosine		×			75
Cyclic guanosine monophosphate			×		64
Chitobiose	×	×	×	×	3,4,64,67,70
Chitotriose	×	×			3,4,70,108
Choline	×		×	×	3,64,65,76,108
Ciliatine	×	×			3,4

Continued

Table 1 | Marine microbial metabolites

Metabolite	Exometabolite in seawater	Exometabolite in culture	Endometabolite in marine plankton	Endometabolite in culture	Refs.
Citrate	×		×		3,64
Citrulline	×	×		×	3,67,75
Creatine			×		64
Cyanocobalamin	×	×			67,108
Cystathionine			×		64
Cysteinolate			×		18
Cysteate	×	×	×	×	4,18,64
Cysteine	×	×			4
Cytidine	×		×		4,64
Cytosine			×		64
Desthiobiotin	×				3,108
Dihydroxyacetone phosphate	×				3
DHPS	×	×	×	×	3,4,18,64,65,69,76
Dimethylglycine			×	×	64,76
Dimethylsulfonioacetate				×	71
DMSP	×	×	×	×	64,65,67,69,73,76,108,116,225,226
Dimethylsulfoxonium propionate	×			×	227
Ectoine	×	×			3,4
Ethanolamine				×	76
Folate	×		×		108,116
Fosfomycin	×				3
Gamma-aminobutyrate	×	×			4
Gluconate			×		64
Glucose				×	76
Glucose-6-phosphate	×			×	3,67,108
Glucosamine-6-phosphate	×	×			4,108
Glucosylglycerol			×	×	64,65
Glutamate	×	×	×	×	3,4,64,65,67,76
Glutamine	×	×	×	×	4,64,65,76,225
Glutathione	×		×	×	3,64,67
Glycerol-3-phosphate	×		×	×	3,64,76
Glycerophosphocholine				×	76
Glycine	×	×		×	4,76
Glycine betaine			×	×	64,65,67,76,116
Glyphosate	×				108
Gonyol			×	×	64,71
Guanine	×		×		3,64,116
Guanosine	×	×	×	×	3,64,70,76,108
Guanosine monophosphate			×		64
Histidine	×	×	×		4,64
Homarine			×	×	64,76
Homoserine	×	×			4
Homoserine betaine		×			4
Hydroxocobalamin			×		64
Indole-3-acetate	×	×	×		64,67,108,116
Indole-3-acetamide			x		64

Continued

Table 1 | Marine microbial metabolites

Metabolite	Exometabolite in seawater	Exometabolite in culture	Endometabolite in marine plankton	Endometabolite in culture	Refs.
Inosine 5′-monophosphate	×				108
Inosine	×	×	×		3,67,70,108,116
Isethionate	×	×	×	×	18,64,65
Isoleucine	×	×	×	×	64,65,70,76,108,116
Kynurenine	×	×	×		3,4,64,108
Leucine	×	x	×	×	3,4,64,70,75,76,108,116
Lysine	×	×	×	×	4,64,65,76
Malate	×	×			3,4
Methionine			×	×	64,116,225
Methylglutarate		×			75
Methyl indole-3-carboxylate			×		64
Muramate	×	×			4
N-(3-oxotetradecanoyl)-L- homoserine lactone		×		×	116
N-acetyl-galactosamine	×	×		×	67,75
N-acetyl-glutamate	×	×			67,108
N–acetylmuramate	×	×			3,4,108
N-acetyltaurine		×			67
N-tetradecanoylaspartate		×			75
Niacin			×		64
Nicotinamide adenine dinucleotide-hydrogen	×				3,108
Nicotinamide adenine dinucleotide-phosphate	×				108
Norvaline		×			75
Oleate		×			75
Ornithine	×	×		×	4,65
Pantothenate	×	×	×		3,4,64,108,116
Phenylacetate		×			75
Phenylalanine	×	×	×		3,4,64,67,108,116
Phosphoglycerate			×		64
Phosphorylcholine				×	76
Proline	×	×	×	×	3,4,64,65,67,70,76,116
Propionate		×		×	225
Putrescine	×	×			4
Pyridoxine	×		×		3,64,116
Pyridoxal			×		64
Pyridoxal phosphate			×		64
Quinolinecarboxylate		×			75
Riboflavin	×	×	×	×	3,64,108,116,225
Ribose 5-phosphate			×		64
Rosmarinate		×			75
S-5′-adenosyl-L-homocysteine	×	×	×		3,4,64
S-adenosyl methionine			×		64
Sarcosine	×	×	×		4,64
Serine		×	×		4,64
Shikimate		×			225
Sperimidine	×	×		×	4,67
Sphingamine		×			75
Stearate		×			75

Continued

Table 1 | Marine microbial metabolites

Metabolite	Exometabolite in seawater	Exometabolite in culture	Endometabolite in marine plankton	Endometabolite in culture	Refs.
Suberate		×			75
Succinate	×	×			3,67
Sucrose			×		64
Sulfolactate			×	×	18,64
Syringate	×				3
Taurine	×		×	×	4,18,64,65
Taurocholate	×	×			3,4,67,108
Thiamin				×	67
Thiamin monophosphate				×	225
Threonine	×	×	×		3,64,75
Thymidine	×	×	×		3,64,67,70
Thymine			×		64
Trehalose			×		64
Trigonelline			×		64
Trimethylamine-*N*-oxide				×	76
Tryptamine	×				3,108
Tryptophan	×	×	×		3,64,67,108,116
Tyrosine	×		×		3,64
Uracil				×	67
Uridine	×	×	×	×	3,64,76
Uridine 5-monophosphate	×				108
Uridine diphosphate-glucosamine			×		64
Uridine diphosphate-glucose			×		64
Valine	×	×	×	×	3,4,64,70,76
Vanillate			×		64
Xanthine	×		×		3,108,116
Xanthosine	×		×		3,4,64,108

Shown are exometabolites identified in seawater and culture medium, and endometabolites identified in cultured cells and plankton communities.

ionization[141] enabled the transfer of polar molecules directly into mass spectrometers. Mass resolution and accuracy have dramatically improved with Fourier-transform-based analysers such as Fourier transform ion cyclotron resonance cells[142] and Orbitrap detectors[143], which now routinely enable mass accuracy to levels below parts per million for thousands of molecules within complex mixtures. Chromatographic columns such as hydrophilic interaction chromatography and new mixed-mode resins can deliver specific fractions of the labile DOC pool for characterization[144]. Moreover, picomoles of individual compounds are sufficient to trigger fragmentation spectra for identification. Although typically less sensitive than MS for molecular detection, NMR provides structural information that better enables identification. Higher-field NMR magnets[145] and advanced small-diameter probes provide better analyte detection with lower salt sensitivity[146], and nanomoles of individual molecules are currently required for structural identification. Two-dimensional NMR approaches[147] have been developed to obtain complete covalent geometry of molecules, sometimes with stereochemistry[148]. Further advances in MS and NMR technology offer promise for improved DOC characterization in the near future, including better data deconvolution strategies[149] and improved methods for integrating data for unknown compound identification[150]. The compounds that have been successfully identified in marine metabolomes (Table 1) represent only a small fraction of total metabolite diversity.

Although MS and NMR offer the best potential for identifying biologically labile molecules in marine DOC, the salt problem has yet to be solved. Derivatization protocols show promise for this challenge, in particular those that target functional groups common in biologically produced compounds (for example, alcohol and amine groups[4] and carbonyl moieties[151]). Recent application of derivatization methods are enabling detection in seawater at nanomolar (NMR and gas chromatography/MS)[152] to picomolar (liquid chromatography/MS)[4] concentrations. Identification of polar metabolites by direct injection of seawater into mass spectrometers has also been demonstrated recently for marine culture media, with limits of detection averaging 600 nM over a range from 10 nM to 3.2 µM (ref. [153]).

Chemical methods are now better able to measure bacterial uptake of labile metabolites. Isotopically labelled compounds can be tracked into individual cells using nano-secondary ion MS[154,155] and chemical-tagging tools[156–159]. As sampling volume requirements decrease and instrument sensitivities increase, single-cell measurements of internal and external metabolites will draw tighter associations between microbes and molecules[160,161]. High-resolution magic-angle spinning NMR probes provide access to real-time

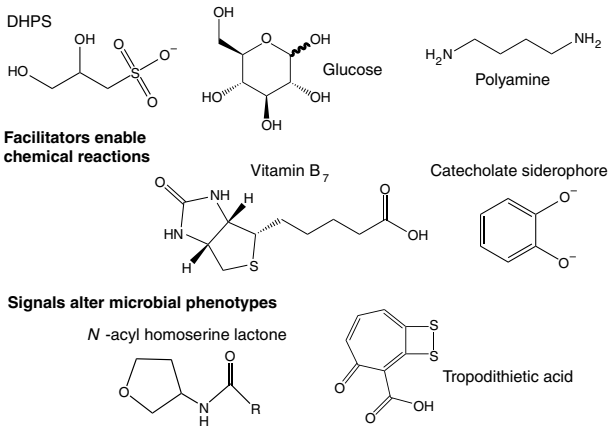
Box 1 | Ecological classes of microbial exometabolites

Metabolites are small molecules that are direct products of metabolism. Chemically, they hail from a wide variety of structural classes and span a range of solubilities, molecular weights and functional groups[229]. Metabolites can also be classified on the basis of their ecological role in microbial communities; in the marine microbiome they typically have one of three main roles, which are outlined below.

Substrate metabolites sustain biomass production and element cycling in microbial communities. In the surface ocean, molecules in this category include carboxylic acids[230,231], glycerols and fatty acids[230,232], nitrogen-containing compounds (such as polyamines)[79,169,230], C_1-compounds[169,230,232], carbohydrates (such as glucose)[7,233], and sulfonates and sulfonium compounds (such as DHPS)[18,69,234]. Substrate metabolites are likely to be synthesized in core biochemical pathways during microbial growth and be conserved across diverse taxonomic groups.

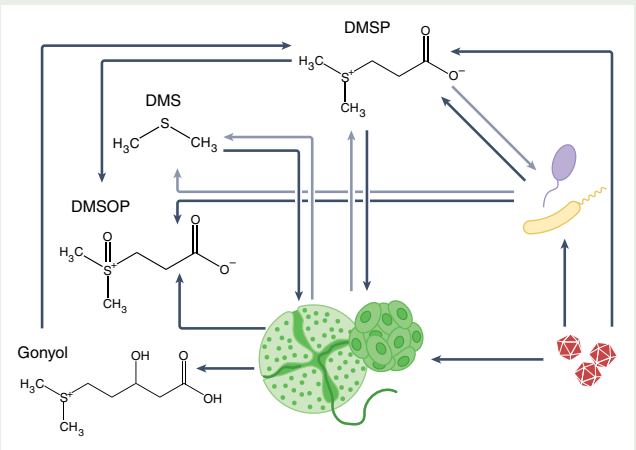
Facilitator metabolites enable or enhance chemical reactions and include molecules such as vitamins (such as B_7) and siderophores (such as catecholate siderophores)[87,235]. Enzymes are considered to be macromolecules rather than metabolites and are not included here. Facilitator metabolites are also likely to be synthesized in core biochemical pathways.

Ecological signal metabolites alter the phenotype of neighbouring microbes and are typically secondary metabolites produced to support non-growth activities. In the marine microbiome, ecological signal metabolites include chemical cues or infochemicals (such as homoserine lactones involved in quorum sensing), microbial pheromones, and antimicrobials and algicides (such as tropdithietic acid)[236–240]. Marine bacteria can devote considerable genomic resources to the synthesis of ecological signal metabolites[241,242].



Box 2 | Hunting marine metabolites

Determining the role of an ocean metabolite is a complex and multidisciplinary process, as revealed by the decades of research dedicated to learning the biogeochemistry of just one metabolite: DMSP. Early research established DMSP as a major phytoplankton osmolyte[226], an important substrate for marine bacteria[243] and the precursor of dimethylsulfide (DMS), which is the dominant volatile in the ocean–atmosphere sulfur flux[244,245]. Yet the biochemical mechanisms of DMSP synthesis and degradation remained unknown until genomic data enabled gene discovery beginning in 2006[246–249]. Since then, the configuration of the microbial–DMSP network, initially considered a simple flux from phytoplankton to bacteria via the labile DOC pool (light arrows), has been revealed as a highly complex web of synthesis and utilization (dark arrows). New network edges have been discovered, such as the findings that bacteria also synthesize DMSP[246] and that phytoplankton also assimilate it from the environment[250]. New nodes have been discovered, such as chemical relatives of DMSP that affect its fate[71,227] and roles for viruses in release and transformation[251,252]. New functions for DMSP have been discovered, such as ecological signals for bacterial chemotaxis[253] and pathogenesis[254]. DMSP may be the highest-flux single metabolite of the surface ocean carbon cycle[73,135], yet biological and chemical studies over decades were required to unravel the intricacies of its dynamics. Factors that regulate the fate of DMSP, including what controls its transformation to climate-active DMS, are yet to be resolved[163,255,256]. DMSOP, dimethysulfoxonium propionate.



metabolism in vivo, even in the presence of high salt concentrations[162]. Flux measurements at the required temporal and spatial scales are on the horizon, with advances in tracking isotope incorporation through intracellular metabolic pathways[163,164], cellular uptake of individual metabolites[162] and fluid-flow devices coupled to high-resolution imaging[137]. These multiple approaches are chipping away at the barriers to progress.

Biological methodological advances. Labile metabolites are defined as those susceptible to microbial transformation, which makes evidence of biological processing an effective operational definition for labile DOC. Biology-based screening approaches fall into two categories: those that use biological signals alone to generate hypotheses regarding important compounds and those that couple biological signals with chemical analysis. In the former category, gene, transcript and protein inventories suggest which molecules are produced and consumed. These biosensor strategies do not require disruption of steady-state interactions and instead survey intact natural communities (using metagenomics, metatranscriptomics and metaproteomics) or model organism systems (using genomics, transcriptomics and proteomics). This approach has offered insight into metabolite flux in phytoplankton blooms[165,166], oligotrophic seawater[167,168], model communities[66,74] and ocean-wide surveys[169,170]. It has been used to construct co-occurrence networks of microbes and metabolites[171,172], and has provided insight into the choreographed daily cycles of metabolite-driven phytoplankton–bacteria interactions in the surface ocean[18,27,167,173] (Fig. 3). The approach can be expanded to regional, global and full-ocean-depth scales to illuminate large-scale patterns in labile DOC transformations. Biological screening methods that rely solely on microbial

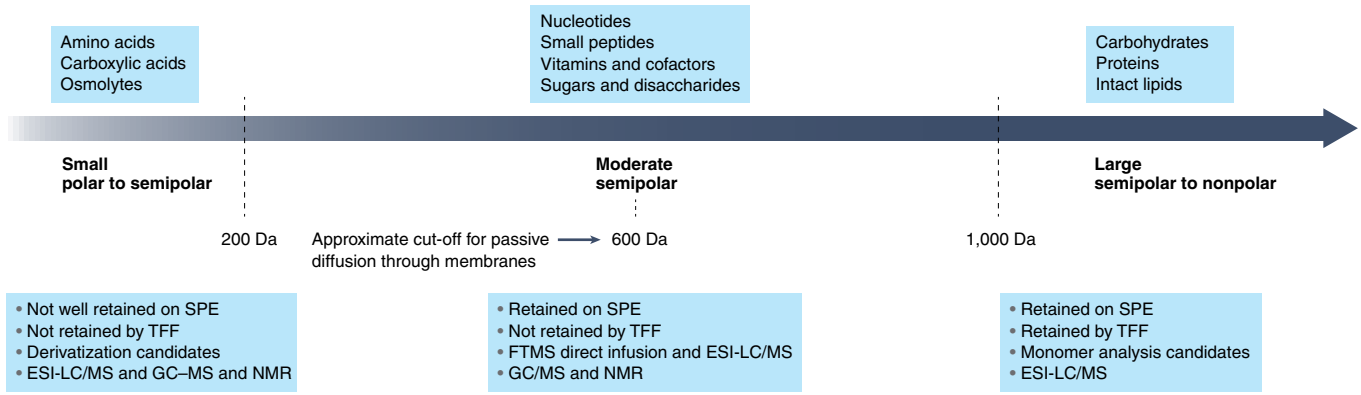


Fig. 4 | The marine DOC spectrum. Chemical analysis strategies for marine DOC are targeted to molecules of different size and hydrophobicity, and typically begin with extraction and concentration from seawater. Solid-phase extraction (SPE) includes common resin types such as C18, C8, hydrophilic–lipophilic balance and priority pollutant. ESI-LC/MS, electrospray ionization-liquid chromatography/MS; FTMS, Fourier transformMS (includes Orbitrap mass spectrometers and Fourier transform ion cyclotron resonance mass spectrometers); GC/MS, gas chromatography/MS.

response, however, are ultimately constrained by inadequate and slowly advancing gene annotation, an area for which investments in technology and new approaches are sorely needed.

The second category of biological screening is coupled to chemical analysis. This typically requires steady-state disruption, altering either the accumulation or utilization of DOC by modifications to the microbial community (for example, removing phytoplankton or bacteria[68,75,100] or adding viruses[45]) or by manipulation of environmental parameters (for example, irradiance[174]), followed by chemical analysis of the altered pools. Drawdown studies introduce bacteria into a DOC pool and rely on chemical analysis to identify features that are depleted[70], such as characterization of bacterial substrate use by different species[70]. Mutant screening studies introduce bacteria with disrupted genes into a DOC pool and rely on chemical analysis to identify features that are no longer depleted, for example, identification of the phytoplankton exometabolite dihydroxypropanesulfonate (DHPS) from its accumulation in a transporter mutant assay[69]. Enzymatic activity assays use selective digestion by high-specificity bacterial enzymes to quantify labile compounds within complex mixtures, for example, hydrolases that degrade laminarin into diagnostic sugar units that are readily measured[175]. Other biological screening strategies that are currently used primarily in the field of biochemistry have promise for adoption in ecological studies. Vesicular transport assays embed transporters in synthetic membrane vesicles in an inside-out orientation, trapping target metabolites in the vesicle for chemical analysis[176]. Metabolite–protein binding assays detect enzymes that bind to known metabolites, for instance, identification of substrates of *Escherichia coli* enzymes that previously lacked functional annotation[177]. Finally, activity-based protein profiling uses chemical probes with reporter tags that mimic metabolites and form covalent bonds with microbial enzymes, for instance, to identify novel catabolic enzymes that degrade cellulose[178]. The coupling of biological screening with chemical tools holds promise for pinpointing the hidden chemical currencies of the surface ocean and the genes and enzymes that transform them.

Modelling microbial metabolism. Modelling approaches are being used to extract carbon-cycle-relevant insights from observations of the microbe–metabolite network of the ocean. The challenge for models is to bridge a spatial scale spanning 13 orders of magnitude, from cell metabolism at the scale of 10^{-6} m to ocean flux at the scale of 10^{7} m. Component models that focus on specific portions of this spatial scale already exist or are being developed. At the microbial end, earlier models of DOC release by phytoplankton sought a mechanistic understanding based on parameters such as phytoplankton size, nutrient status and photosynthetic output[179–181]. More recent models use genomic data to address the biochemical basis for metabolite production and consumption. Metabolic models based on flux balance analysis[182] typically optimize for generation of new biomass, but could optimize for other physiological or ecological traits[183] such as metabolite release, abiotic stress tolerance or carbon use efficiency[184]. Phylometabolic modelling integrates comparative genomics with insights from biochemistry and ecology to reconstruct metabolic innovations that affect metabolite production and consumption, such as complementary organic matter exchange between phytoplankton and bacteria[17]. Multicell metabolic models for single colonies or multispecies communities[185] uncover rules governing metabolite exchange and provide parameters for models working at regional to global scales[186,187].

In the transition from cellular scales to regional and global scales, hard-fought details of metabolite chemistry and biology must be simplified but not trivialized. The need to identify the optimal balance between excessive detail and oversimplification has emerged as a crucial barrier to incorporating microbial processes into global models[188], along with high computational costs, limited conceptual foundation, and lack of data to formulate and evaluate the more complex models. Nonetheless, global and regional DOC dynamics can be captured through nutrient–phytoplankton–zooplankton–detritus (NPZD) modules, which are widely used to compare historical and future climates[189,190]. These models approximate the details of microbe–metabolite networks with bulk functions (such as Michaelis–Menten equations for substrate uptake) and use simplified rules to track substrates and energy through core metabolic pathways[189]. Conceptual convergence between models at different scales can potentially be leveraged, for example, by linking cell growth output from steady-state flux balance analysis models with resource allocation rules applied to NPZD models.

The recently developed 'emergent' models, in which microbial community structure and function emerge from a wider set of possibilities, combine microbial genomic or physiological data with a dynamic physical–chemical ocean model to observe biogeochemical outcomes. Outputs from emergent models have revealed, for example, a predictable assembly of communities based on functional repertoire rather than taxonomic affiliation[191] and matched distributions and abundance of model microbes with their real-world counterparts across ocean light and temperature gradients[192]. An inherent struggle with these models is parameterizing the bioenergetic cost of a gene or gene function[191,193,194]. More work is needed to overcome these challenges, but it is clear that successful modelling

of labile DOC flux at regional and global scales will close one of the largest knowledge gaps in the global carbon cycle.

Computational data science approaches. Software solutions that respond to the needs for interdisciplinarity and integration in microbiome science are emerging[195–198], including those that build microbe–metabolite networks with machine-learning tools[199]. Other strategies address metabolite-related gene annotation by merging information on 'genes without a metabolite' with information on 'metabolites without a gene'. For example, the metabolite annotation and gene integration (MAGI)[200] method identifies patterns of metabolite–gene associations by scoring the consensus in occurrence between the two datasets. The crowd-sourced Global Natural Product Social Molecular Networking (GNPS)[201] database improves metabolite identification and annotation by enabling comparisons of fragmentation spectra. Finally, the Paired Omics Data Platform links matched genomic and metabolomic data deposited in public repositories[202]. As annotations improve, in silico reconstructions can serve as knowledge repositories that facilitate data integration of reactions and pathways and enable predictions of microbial biosynthetic capabilities as environmental conditions, genetic perturbations and fitness functions[111,203,204] vary. These informatic-centric approaches offer starting points for improved inventories of the microbial metabolites and identification of genes with important roles in surface ocean carbon flux.

Despite both progress and interest, the ability to co-investigate chemical compounds and their genetic determinants across space and time remains a bottleneck to characterizing microbe–metabolite networks. Data sharing is imperative among marine chemists and microbiologists to enable discoverability, integration and interoperability of data across software tools. Moreover, data exchange through software is necessary to leverage a growing public database that merges marine bacterial, archaeal and eukaryotic genomes[205,206], metagenomes[207–209], metatranscriptomes[210] and metaproteomes[211], and annotation resources for chemical oceanography[201,212]. Integrative strategies will lead to characterization of the genes that link microbial activity to the production and consumption of key metabolites.

Microbial currencies in a warming ocean

The well-recognized downward export of particulate organic carbon from the surface ocean to deep ocean waters and sediments (the 'biological carbon pump') is globally important because it isolates carbon from the atmospheric pool for hundreds to thousands of years[213,214]. The microbial remineralization of labile carbon to its inorganic form is globally important because it diverts carbon from the biological carbon pump, reducing net community production and influencing air–sea CO_2 fluxes[215,216]. The quantitative importance of labile DOC remineralization becomes clear by considering that it constitutes >0.1% of the total DOC pool yet accounts for 86% of total DOC turnover[2]. This implies that rapidly cycled microbial metabolites are among the most important individual conduits of ocean carbon.

Recent studies have provided a framework for predicting how phytoplankton-derived components of labile DOC might be altered under future climate scenarios, despite often complex and species-specific responses. Increasing temperature has been shown to enhance total carbon release by phytoplankton[15]. Evidence suggests that increased ribosome efficiency under higher temperatures will decrease phosphorus demand[217–219] and will lower the N:P stoichiometry of labile DOC as rRNA synthesis needs are lessened. Mismatches between phytoplankton photosynthetic flux (weakly affected by temperature) and metabolism (strongly affected by temperature) can have diverse impacts on cellular resource allocation and metabolism[219]. Increased CO_2 concentrations can decrease photorespiration rates and alter the release of photorespiration products such as glycolate[220,221]. Finally, a warming climate is predicted to favour smaller phytoplankton cells, which are better able to compete for nutrients in a stratified ocean[222,223], shifting labile DOC chemistry towards metabolite profiles characteristic of cyanobacteria and green algae[18,224]. As these predictions are being formulated, the microbial functions underlain by the production and cycling of the substrates, facilitators and ecological signals exchanged via the labile DOC pool are being recognized.

Conclusion

Details of the metabolic currencies that transfer carbon between microbes to sustain the surface ocean carbon cycle have until recently been largely invisible to scientists. Importantly, climate–carbon feedback loops mediated by the labile DOC reservoir depend on this microbe–metabolite network. The resilience of the ocean to planetary change will rely on responses of the network to temperature increases, ocean acidification and other linked environmental changes. With advances in the chemical, biomolecular and data sciences, more of these nearly invisible molecules and their roles in the ocean carbon economy are being recognized. The future promises rapid scientific advances in understanding the chemical currencies of the surface ocean carbon cycle, at a time when increased knowledge is needed to safeguard against the effects of global change.

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