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ARTICLE





Sulfur metabolites that facilitate oceanic phytoplankton-bacteria carbon flux

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Abstract

Unlike biologically available nitrogen and phosphorus, which are often at limiting concentrations in surface seawater, sulfur in the form of sulfate is plentiful and not considered to constrain marine microbial activity. Nonetheless, in a model system in which a marine bacterium obtains all of its carbon from co-cultured phytoplankton, bacterial gene expression suggests that at least seven dissolved organic sulfur (DOS) metabolites support bacterial heterotrophy. These labile exometabolites of marine dinoflagellates and diatoms include taurine, *N*-acetyltaurine, isethionate, choline-O-sulfate, cysteate, 2,3-dihydroxypropane-1-sulfonate (DHPS), and dimethylsulfoniopropionate (DMSP). Leveraging from the compounds identified in this model system, we assessed the role of sulfur metabolites in the ocean carbon cycle by mining the Tara Oceans dataset for diagnostic genes. In the 1.4 million bacterial genome equivalents surveyed, estimates of the frequency of genomes harboring the capability for DOS metabolite utilization ranged broadly, from only 1 out of every 190 genomes (for the C2 sulfonate isethionate) to 1 out of every 5 (for the sulfonium compound DMSP). Bacteria able to participate in DOS transformations are dominated by Alphaproteobacteria in the surface ocean, but by SAR324, Acidimicrobiia, and Gammaproteobacteria at mesopelagic depths, where the capability for utilization occurs in higher frequency than in surface bacteria for more than half the sulfur metabolites. The discovery of an abundant and diverse suite of marine bacteria with the genetic capacity for DOS transformation argues for an important role for sulfur metabolites in the pelagic ocean carbon cycle.

Supplementary information The online version of this article (https://doi.org/10.1038/s41396-019-0455-3) contains supplementary material, which is available to authorized users.

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Introduction

The trophic linkage between marine bacteria and phytoplankton in the ocean represents a key step in the global carbon cycle, with phytoplankton lysis products [1] and "dissolved primary production" [the dissolved organic carbon (DOC) released from living phytoplankton [2]] supporting a major fraction of labile carbon flux. Approximately 20 Gt of labile DOC are turned over by heterotrophic marine bacteria each year, an amount more than an order of magnitude higher than the annual turnover from the semi-labile and refractory marine DOC pools combined [3].

Sulfur is a component of amino acids, sulfolipids, and other biomolecules essential to marine bacteria, but the high inorganic sulfur concentration in seawater (~28 mM SO₄⁻²) suggests that its availability is not an important factor governing microbial growth. However, discoveries that members of the ubiquitous SAR11 and SAR86 bacterial clades are incapable of assimilating sulfate and thus

dependent on uptake of organic sulfur [4, 5] bring a new perspective to the role of dissolved organic sulfur (DOS) in microbial heterotrophy. Overall, little is currently known about the availability or trophic fate of DOS compounds in the ocean. The one exception is the sulfonium compound dimethylsulfoniopropionate (DMSP), a DOS metabolite synthesized by phytoplankton as an osmoprotectant, possible antioxidant [6], and possible predator deterrent [7] that is readily utilized by heterotrophic marine bacteria [8].

An improved understanding of the participation of labile DOS in the carbon cycle requires better knowledge of the phytoplankton-derived molecules supporting the metabolism of heterotrophic bacteria. These molecules have proven difficult to identify, however, because efficient bacterial scavenging drives their concentrations into the picomolar range [9, 10] and their half-lives in seawater down to minutes [11]. An alternative strategy for discovering the molecular currencies supporting microbial heterotrophy is to extract biological signals from bacterial messenger RNA (mRNA) [12–14]. In this approach, the transcriptional responses of bacteria to phytoplankton-derived metabolites provide indications of substrate uptake and metabolism.

We previously established a model system to investigate how the compounds supporting bacterial heterotrophy varied with changes in the dominant phytoplankton taxon. The transcriptional response of marine bacterium Ruegeria pomeroyi DSS-3 was measured when co-cultured first with the dinoflagellate Alexandrium tamarense and then with the diatom Thalassiosira pseudonana [15]. Bacterial gene expression patterns indicated that both phytoplankton species were releasing labile DOS metabolites into the medium. At a minimum, these included 2,3-dihydroxypropane-1sulfonate (DHPS), taurine, *N*-acetyltaurine, and DMSP [15]. In this study, we follow-up on these initial results using data from this co-culture system and metagenomic data from the TARA Oceans expedition [16] to answer two questions: (1) What does bacterial gene expression reveal about the identity of labile phytoplankton-derived DOS metabolites? (2) What is the abundance, taxonomy, and distribution of the ocean bacterioplankton capable of utilizing these metabolites? Our results show that at least seven phytoplankton-derived DOS metabolites can support bacterial heterotrophy, and indicate a more important role for DOS in microbial trophic interactions and carbon flux than previously recognized.

Methods

Experimental setup

Axenic strains of the dinoflagellate *A. tamarense* CCMP1771 and diatom *T. pseudonana* CCMP1335 were

obtained from the National Center for Marine Algae and maintained with regular checks for bacterial contamination by microscopy and plating [15]. Co-cultures of the phytoplankton with or without the bacterium R. pomerovi DSS-3 were established in six 20-L LDPE cubitainers (Reliance, Winnipeg, Canada). The cubitainers were first filled with 18 L of autoclaved, 0.2-um-filtered Guillard's f/2 medium with vitamin B₁₂ added at f/50 concentration and 2 L of an axenic A. tamarense culture in exponential phase grown in the same medium. The f/2 medium contained $880 \,\mu\text{M}\,\text{N}$ as NO_3^- and $36 \,\mu\text{M}$ P as PO_4^{-3} at the time of inoculation. Cubitainers were maintained at 18 °C with a 16-8 h light-dark cycle under ~160 µmol photons m⁻² s⁻¹. After 7 days, bacteria grown overnight in ½YTSS medium were harvested in exponential phase, washed five times with sterile phytoplankton medium, and added to three of the cultures at $\sim 10^5$ cells ml⁻¹. Five days later, axenic T. pseudonana in exponential phase grown in the same modified f/2 medium was added to all cubitainers at 200 cells ml⁻¹ along with silicate at 100 µM final concentration. The order in which the phytoplankton were introduced was determined based on T. pseudonana's ability to outcompete A. tamarense under the culture conditions used. The cultures were maintained for 37 days [15].

Sampling and monitoring

Samples were taken regularly from the cubitainers and streaked onto ½YTSS plates to check for bacterial growth. Plates from bacteria-free phytoplankton controls were checked for growth of any bacteria, while plates from experimental cubitainers were visually inspected for colonies with different morphology from R. pomeroyi. No contamination was detected throughout the 37-day experiment. Bacterial and phytoplankton cell numbers were monitored in the cubitainers by flow cytometry. Triplicate samples were preserved in glutaraldehyde (2% final concentration), stained with SYBR® Green I (final concentration 0.75x; Life Technologies, Waltham, MA, USA), and analyzed on a Cyan instrument (Beckman Coulter, Brea, CA, USA) using the FlowJo software [15]. On days 7, 9, 12, 15, 18, 23, 30, and 37, 1 L samples were collected for chemical analyses and RNA-sequencing (RNA-seq).

Chemical analyses

Duplicate 6 ml samples filtered through 0.45-µm hydrophilic polyethersulfone Acrodisc Supor membranes (Pall Life Sciences, Port Washington, NY, USA) were analyzed for dissolved inorganic nitrogen (nitrate + nitrite) (APHA Standard Method 4500-NO₃ F), ammonium (4500-NH₃ G), dissolved inorganic phosphorus (4500-P F), and silicate (spectrophotometric silicomolybdate assays). Triplicate

samples that were unfiltered or filtered through ashed Whatman GF/F filters were combusted on a Shimadzu TOC-5000A Analyzer to determine total organic carbon (TOC) and dissolved organic carbon (DOC) concentrations, respectively. Analyses were performed at the Center for Applied Isotope Studies (University of Georgia, Athens, GA, USA).

DMSP was the only organic sulfur metabolite measured in the co-culture medium. For total DMSP analysis, 10 ml subsamples were collected in 15 ml polypropylene tubes with plug seal caps (Corning, NY, USA) containing HCl (1.5% final concentration) for preservation. For dissolved DMSP analysis, 10 ml samples were gently poured into a polysulfone filtration tower equipped with a 25 mm GF/F filter, and 4 ml were gravity filtered and preserved in 1.5% HCl. At the time of analysis, DMSP was cleaved into dimethylsulfide (DMS) by the addition of NaOH (1.3 M final concentration). Resulting DMS was quantified using a gas chromatograph (Shimadzu GC-2014 or GC-14A) with a Chromosil 330 column and a flame photometric detector coupled with a purge and trap system [17].

Bacterial RNA extraction and RNA-seq

Bacterial cells were collected on $0.2 \, \mu m$ pore-size poly-carbonate (PC) membranes after pre-filtration of 1 L samples through $2 \, \mu m$ pore-size membranes to remove eukaryotic cells [15]. Filters were flash frozen in liquid nitrogen and stored at $-80 \,^{\circ}\text{C}$. For RNA extraction, filters were incubated at $37 \,^{\circ}\text{C}$ for 1 h in TE buffer, sodium dodecyl sulfate (0.6% final concentration), and proteinase K (120 ng μl^{-1} final concentration, Qiagen, Hilden, Germany). An extraction with acid phenol:chloroform:isoamylalcohol was performed, and RNA was resuspended in RNAse-free water. RNA was precipitated with sodium acetate (0.3 M final concentration) and three volumes of 100% ethanol, and incubated overnight at $-20 \,^{\circ}\text{C}$. Pellets were washed twice with 75% ethanol, centrifuged, dried, and resuspended in RNAse-free water [15].

Samples were treated with the Turbo DNA-free kit (Invitrogen, Waltham, MA, USA) to remove DNA, and tests for residual DNA by a 40-cycle PCR targeting the 16S ribosomal RNA (rRNA) gene of *R. pomeroyi* were negative. rRNA was depleted using custom probes for small and large subunit rRNA genes from all three microbes [18]. Libraries were prepared for two replicate cubitainers at each time point using the KAPA Stranded mRNA-Seq kit (Kapa Biosystems, Wilmington, MA, USA) at the Georgia Genomics and Bioinformatics Core (University of Georgia) and sequenced on a HiSeq Illumina 2500 at the Hudson Alpha Institute for Biotechnology (AL, USA).

RNA-seq analysis

The FASTX toolkit was used for quality control of 249 million 50-bp reads $(10 \pm 2 \text{ million reads per sample};$ Table S1), imposing a minimum quality score of 20 over 80% of read length. Reads aligning to an in-house rRNA database were removed (blastn, score cutoff ≥50). Bowtie 2 [19] and HTSeq [20] were used to map the remaining reads to the R. pomeroyi genome, conserving strand information and removing reads that mapped to more than one location (Table S1). Counts were converted to transcripts per million [TPM [21]; Table S2] and data deposited in the NCBI BioProject database under accession PRJNA381627. Genes with differential expression between selected time points (representing diatom- and dinoflagellate-dominated phases) were determined with DESeq2 [22]. Although bacterial expression can change more rapidly than the time intervals between samples, genes identified as significantly different were consistent over multiple sample dates within each phase and most likely represented sustained transport/ metabolism activities.

Ruegeria pomeroyi expression assays

In a separate experiment, *R. pomeroyi* was grown in a minimal medium with 12 mM choline-O-sulfate, 20 mM cysteate, or 30 mM acetate as the sole substrate. Overnight cultures were pelleted by centrifugation, resuspended in 1 ml Ambion (Thermo Fisher Scientific) denaturation solution, flash frozen in liquid nitrogen, and stored at -80 °C until RNA extraction. Samples were treated with the TURBO DNA-free kit to remove DNA and Ribo-Zero-Bacteria (Illumina) to remove rRNA. Library preparation, sequencing, and differential expression analysis were as described above.

Mining of the TARA Oceans metagenomes

We analyzed 225 TARA Oceans metagenomes in the bacterial/archaeal size range, either 0.22–1.6 or 0.22–3 µm, from surface (SRF), deep chlorophyll maximum (DCM), and mesopelagic (MES) depths (Table S3). Accounting for replicate samples, 132 unique stations/depths were analyzed. The metagenomes were assembled using SPAdes version 3.9 using k-mers of 21, 33, 55, and 77 after standard adapter trimming and error correction using BFC (https://github.com/lh3/bfc) with the k-mer size set to 19. The reassembly pipeline built contigs within individual samples, allowing coverage calculation by station and depth. Genes were called using Prodigal version 2.6.3 with default parameters. Coverage was obtained using BWA (https://github.com/lh3/bwa) with default parameters to map reads

back to contigs and samtools (https://github.com/samtools/samtools) to calculate coverage for each contig.

Hidden Markov Models (HMMs) were used to search the contigs for DOS genes. The HMMs were constructed from reference sequences from bacterial isolates obtained for 11 DOS-related genes that were differentially expressed by R. pomerovi during the co-culture experiment. Proteins with experimentally verified function were used whenever possible (Table S4). These gene databases were used to build the HMMs using HMMER 3.1b2. From the output from each HMM run against the gene calls in the Tara contigs, only sequences with at least 40% protein identity to a reference gene were kept. A score was then determined where at least 80% of assembled genes were manually annotated as the correct gene based on blastP analysis and tree building (Table S4). Most of the DOS-related genes mediate transformations in catabolic pathways, although transporter substrate binding genes were used in the case of the three C2 sulfonates that have a shared catabolic pathway. We note that our estimates of DOS gene frequencies are conservative, since HMM cutoffs were stringent, and any alternate pathway or transport proteins would not be counted. The Tara dataset was also searched for the singlecopy gene recA using the HMM in the Pfam Database (http://pfam.xfam.org/family/PF00154#tabview=tab0).

Relative gene abundance information was obtained for each DOS gene and *recA* based on coverage of the Tara contigs. The proportion of cells harboring a DOS gene at a given location and depth was estimated as: DOS gene counts (normalized to the length of the *recA* gene)/*recA* gene counts. A Bray–Curtis dissimilarity analysis based on DOS gene abundances by sample was carried out in R (vegan package, vegdist function) [23].

Taxonomy information was obtained for the gene assemblies that passed the HMM cutoff using Diamond [24] against the May 2018 version of the IMG non-redundant database by keeping the taxonomy of the best hit. In cases of frequent taxonomy assignments to a bacterial group not previously known to possess the genetic capability, manual annotation of gene function and that of its neighboring genes was carried out. Neighboring genes were also classified taxonomically to check for evidence of misassembled contigs, but this was not found.

Results and discussion

Co-culture dynamics

Dinoflagellate *A. tamarense* was the only phytoplankton species in the co-cultures until day 12, when diatom *T. pseudonana* was inoculated. *Thalassiosira pseudonana* became numerically dominant by day 18, and was the only

phytoplankton species detected by day 30 (Fig. 1a). As described in Landa et al. [15], the bacterium R. pomeroyi was inoculated into three phytoplankton cultures on day 7 at a concentration of 3.7×10^5 cells ml⁻¹ and increased in abundance by 32-fold by day 37 (Fig. 1b). Bacterial growth was sustained solely by phytoplankton exometabolites since no exogenous carbon or nitrogen sources usable by the bacterium were provided. The remaining three phytoplankton cultures were left bacteria free. DOC and TOC increased over time in both conditions, but were lower in the co-cultures with bacteria (Fig. 1c, d). Inorganic nitrogen and phosphorus were gradually drawn down during the experiment, but remained high enough to ensure that phytoplankton growth was not limited by either nitrogen or phosphate availability (Fig. S1). There was no difference in phytoplankton cell dynamics between treatments with and without bacteria (Fig. 1a).

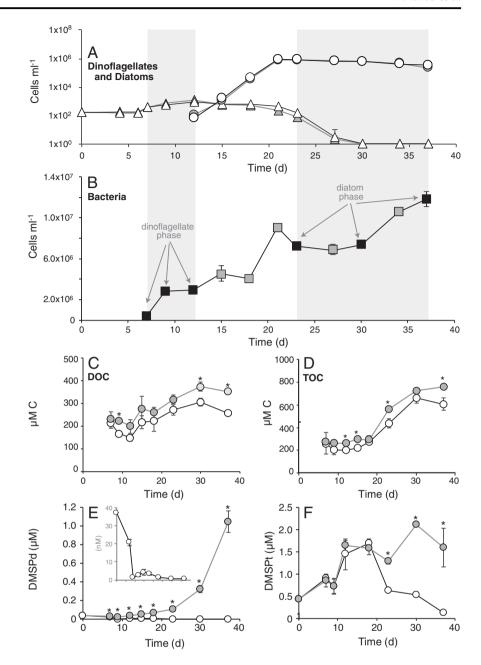
Data from this co-culture system served as the basis to investigate the role of phytoplankton-derived DOS metabolites in supporting heterotrophic bacterial growth and activity. An early co-culture phase was defined based on dinoflagellate dominance and encompassed sampling days 7, 9, and 12; and a late phase was defined by diatom dominance and encompassed days 23, 30, and 37 (Fig. 1b). Bacterial genes with experimentally confirmed roles in DOS utilization were tested for differential expression during growth with the two phytoplankton species (Table 1).

Sulfonate metabolism

Expression patterns indicated that five sulfonates, a class of organic sulfur compounds characterized by a R-SO $_3$ ⁻ functional group, were likely serving as substrates for R. pomeroyi growth in the co-cultures. Transcripts for the transport and catabolism of the C3 sulfonate DHPS were enriched during the diatom-dominated phase of the co-culture, including those encoding uptake (hpsKLM) and catabolism to cysteate (hpsOPN, slcD) and pyruvate plus sulfite (cuyA) (Fig. 2a; Table 1). DHPS was previously identified as an abundant metabolite in T. pseudonana [25–27] and was also found in the dissolved organic matter pool associated with a marine diatom bloom [27].

We noticed enrichment of transcripts from an operon containing an unannotated ABC transporter (SPO2658-2661) and an adjacent gene (SPO2657) having high identity to *cuyA*, the gene that encodes L-cysteate sulfolyase in the DHPS catabolism pathway [28] (Table 1). Based on the function of L-cysteate sulfolyase, we hypothesized that the C3 sulfonate cysteate was also available as a bacterial substrate during the diatom-dominated co-culture, and transported into the cell by the upregulated unannotated transporter system (Fig. 2a). Transcriptional analysis of *R. pomeroyi* grown on cysteate compared to acetate showed

Fig. 1 Cell abundance and chemical data from the model system, a Dinoflagellate (triangles) and diatom (circles) cell abundances in co-cultures (white symbols) and axenic cultures (gray symbols). b Bacteria cell numbers in cocultures, with time points of transcriptional analysis indicated by black symbols. c-f Concentration of dissolved organic carbon (DOC), total organic carbon (TOC), dissolved dimethylsulfoniopropionate (DMSP) (DMSPd), and total DMSP (DMSPt) in co-cultures (white symbols) and axenic cultures (gray symbols). The inset in e shows DMSPd concentrations in the co-culture treatment at a resolved scale. n = 3 for all measurements. Standard deviations falling within the height of the symbol are not shown. Asterisks indicate significant differences (p < 0.05)



strong upregulation of the ABC transporter components and adjacent *cuyA*-like gene (*cuyA*-2; Fig. S2), supporting a role in cysteate utilization. As is the case for *cuyA* in the DHPS pathway, *cuyA*-2 is predicted to oxidize cysteate to pyruvate and sulfite, although cysteate catabolism provides a net source of ammonium to the bacterium, whereas DHPS does not (Fig. 2a). While sulfonate concentrations were not measured in this study, previous studies showed cysteate to be a component of diatom metabolomes [25, 29].

Co-culture transcription patterns indicated that R. pomeroyi growth was likely supported by three other sulfonates, in this case C2 sulfonates released during the dinoflagellate-dominated phase (Fig. 2b). Seventeen genes

in the *R. pomeroyi* genome have been experimentally confirmed to transport and catabolize the structurally related C2 sulfonates taurine, *N*-acetyltaurine, and isethionate [30–32] (Fig. 2b). These are catabolized through a shared lower pathway leading from sulfoacetaldehyde to acetyl-CoA (via genes *xsc* and *pta*), and this pathway was enriched in the bacterial transcriptome. The isethionate transporter components (*iseKLM*) and upper pathway genes for isethionate, taurine, and *N*-acetyltaurine (*iseJ* and *tpa*; Fig. 2b) were also significantly enriched during the dinoflagellate phase (Table 1). These bacterial expression results are supported by previous findings of both taurine [33] and isethionate [34] in metabolomes of marine diatoms. Here,

Table 1 Expression of sulfur metabolism genes by Ruegeria pomeroyi in the three-member model system

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SPOADS dund Abded juncappropriately CAA del placegonses [63] -1.2 SPOADS dunD Medaly juncappropriately CAA del places [63] -1.2 SPOADS megd Medaly interested oxidase [64] 1.2 SPOADS dalap DASP lyane [67] -1.6 SPOADS nand Archberlock CAA general CA	SPO3804 SPO3805 SPO4018 SPO4018 SPO40269 SPO1299 SPO1299 SPO1294 SPO1914 SPO0660 SPO0660 SPO0660 SPO0660 SPO0667 SPO0677 SPO0677 SPO0677 SPO0678 SPO0679 SPO0679 SPO0690	dmdD megL mooX dddW dddW dddD addQ prpE acul naaR naaB naaB		[64]	-1.2	0.404
SFOOKS1 denial Methylithescriptiot, Cot A bystanes [63] —1.2 SFOAKD2 and M Methylithescriptiot, Cot A bystanes [63] 1.5.7 SFOAKD2 and M DAKSP tyses [63] 1.5.7 SFOAKD2 dad M DAKSP tyses [63] 1.1.5 SFOOXD3 dad M DAKSP tyses [63] 1.1.5 SFOOXD4 dad M DAKSP tyses [63] 1.1.5 SFOOXD4 and M Arryther-Cot disease [63] 1.1.5 SFOOXD5 naad Arryther-Cot disease [63] 1.1.5 SFOOXD5 naad Arrythumine ARC trasporter, pertilsante [70] 1.1.5 SFOOXD5 naad Arracyllumine ARC trasporter, pertilsante [70] 1.1.5 SFOOXD5 naad Transplanter, pertilsante [70] 1.1.5 SFOOXD5 naad Transplanter, pertilsante [70] 1.1.5 SFOOXD5 naad Transplanter, pertilsante [70] 1.1.5 SFOOXD5 naad<	SPO3805 SPOA0318 SPOA0318 SPOA0369 SPO0453 SPO1703 SPO1703 SPO1596 SPO1596 SPO0659 SPO0664 SPO0664 SPO0665 SPO0665 SPO0667 SPO0667 SPO0677 SPO0675 SPO0675 SPO0675 SPO0675 SPO0675 SPO0678 SPO2359 SPO2359 SPO3561 SPO3562 SPO0590	dmdD megL nnoX dddW dddD dddP dddP addQ ppE ppE acul naaR naaA naaB	3-Methylmercaptopropionyl-CoA dehydrogenase	[63]	-1.2	0.747
SPOADON SIST mode of the Methorine gamme byses [65] 1.3 SPOADOS Mode of	SPOA0318 SPOA0269 SPOA0269 SPO1703 SPO1703 SPO1914 SPO01996 SPO0669 SPO0660 SPO0660 SPO0667 SPO0667 SPO0675 SPO0675 SPO0675 SPO0675 SPO0675 SPO0675 SPO0675 SPO0678 SPO0678 SPO0678 SPO0678 SPO0678 SPO0678 SPO0678 SPO0678 SPO0679 SPO0699 SPO0699 SPO0699 SPO0699 SPO0699 SPO0699 SPO0699	megL mioX dddW dddD ddaP dddQ ppE acul naaR naaA naaB	Methylthioacryloyl-CoA hydratase	[63]	-1.2	0.715
SPONOMS mank Melamenthed oxidase [45] 18.7 SPONOMS 440P DNSP yase [67] -1.6 SPONOMS 440P DNSP yase [67] -1.6 SPONOMS 440P DNSP yase [63] 1.1 SPONOMS 440P Avrybit-Cov relatione [63] 1.3 SPONOMS 440P Novelylamine ARC trapporte, profileant [70] 1.3 SPONOMS 440P Novelylamine ARC trapporte, profileant [70] 1.1 SPONOMS 440P Novelylamine ARC trapporte, profileant [70] 1.1 SPONOMS 440P Novelylamine and objectives [70] 1.1 SPONOMS 440P Tramine ARC trapporte, profileant [70] 1.1 SPONOMS 440P Tramine ARC trapporte, profileant [70	SPOA0269 SPOA0453 SPO1703 SPO1703 SPO12299 SPO1396 SPO01914 SPO0660 SPO0661 SPO0663 SPO0663 SPO0667 SPO0674 SPO0675 SPO0675 SPO0675 SPO0675 SPO0675 SPO0678 SPO0578 SPO0580 SPO0580 SPO0590	mtoX dddW dddD ddddP dddQ pvpE acul naaR naaA naaB	Methionine gamma-lyase	[65]	1.3	0.178
SPOOLAS dalah DMSP yase [66] 2.5.7 SPOOL290 dalah DMSP yase [67] -1.6 SPO2290 dalah DMSP yase [68] 1.7 SPO2290 dalah DMSP yase [68] 1.7 SPO2290 dalah DMSP yase [67] 1.1 SPO2290 dalah Acrybry CoAr relatione [67] 2.1 SPO2650 manh Pranscriptional regulant [70] 3.0 SPO2661 manh Pranscriptional regulant [70] 1.3 SPO2662 manh Praceylamine ABC trasporter, premises [70] 1.2 SPO2663 manh Praceylamine ABC trasporter, premises [70] 1.2 SPO2664 manh Praceylamine ABC trasporter, preplamine [70] 1.1 SPO2665 manh Praceylamine ABC trasporter, preplamine [70] 1.1 SPO2667 manh Praceylamine ABC trasporter, preplamine [70] 1.1 SPO2675 manh Praceylam	SPO0453 SPO1703 SPO2299 SPO1596 SPO1914 SPO1914 SPO0659 SPO0660 SPO0660 SPO0660 SPO0660 SPO0667 SPO0674 SPO0675 SPO0675 SPO0675 SPO0675 SPO0675 SPO0578 SPO2356 SPO2356 SPO2356 SPO2356 SPO0599 SPO0590	dddW dddD dddQ prpE acul naaR naaB naaB	Methanethiol oxidase	[45]	15.7	<0.001
SPOT 751 data DMSP base [67] -1.6 SPOT 752 data DMSP base [68] -1.1 SPOT 554 data DMSP base [68] 1.1 SPOT 554 and Analysin Contained [67] 1.1 SPOT 554 and Analysin Contained [77] 1.5 SPOT 554 and Anarcylaturine ABC transporter, portubante [79] 1.8 SPOM 555 nand Anarcylaturine ABC transporter, portubante [79] 1.0 SPOM 556 nand Anarcylaturine ABC transporter, portubante [79] 1.1 SPOM 557 nand Anarcylaturine ABC transporter, portubante [79] 1.1 SPOM 558 nand Anarcylaturine ABC transporter, portubante [79] 1.1 SPOM 550 nand Anarcylaturine ABC transporter, portubante [79] 1.1 SPOM 550 nand Anarcylaturine ABC transporter, portubante [79] 1.1 SPOM 550 nand Anarcylaturine ABC transporter, portubante [79] 1	SPO1703 SPO2299 SPO2299 SPO1596 SPO2659 SPO0661 SPO0662 SPO0663 SPO0663 SPO0664 SPO0663 SPO0664 SPO0664 SPO0663 SPO0675 SPO0673 SPO2356 SPO2356 SPO2356 SPO03561 SPO3560 SPO0590 SPO0590 SPO0590 SPO0590 SPO0590 SPO0590 SPO0590 SPO0590	dddP dddP dddQ prpE acul naaR naaA naaB	DMSP lyase	[99]	25.7	<0.001
SPONDASO dalatip DIMSP passe [68] 1.1 SPONDASO dalatig DIMSP passe [69] 1.1 SPONDASI pontal Arazylue Cook Rigose [63] 1.1 1.50 SPONDASI mand Transcriptional regulance [70] 3.0 1.1 SPONDASI mand Nacacylamine ABC transporter, permease [70] 1.0 1.0 SPONDASI mand Nacacylamine ABC transporter, permease [70] 1.0 1.0 SPONDASI mand Nacacylamine ABC transporter, permease [70] 1.0 1.0 SPONDASI mand Nacacylamine ABC transporter, ATP binding [70] 1.1 1.0 SPONDASI mand Transine ABC transporter, ATP binding [70] 1.1 1.1 SPONDASI mand Transine ABC transporter, ATP binding [70] 1.1 1.1 SPONDASI mand Transporter, ATP binding [70] 1.1 1.1 SPONDASI mand Transcriptional regulance [70] </td <td>SP02299 SP01596 SP01914 SP01659 SP01666 SP00660 SP00661 SP00662 SP00663 SP00663 SP00664 SP00663 SP00664 SP00663 SP00664 SP00663 SP00664 SP00663 SP00663 SP00663 SP00663 SP00676 SP00736 SP00376 SP00376 SP00376 SP00376 SP00376 SP00376 SP00590 SP00590 SP00590 SP00590 SP00596 SP00596 SP00596 SP00596 SP00596 SP00596 SP00596 SP00596 SP00596 SP00596</td> <td>dddQ dddQ prpE acul naaR naaB naaB</td> <td>DMSP lyase</td> <td>[67]</td> <td>-1.6</td> <td>0.091</td>	SP02299 SP01596 SP01914 SP01659 SP01666 SP00660 SP00661 SP00662 SP00663 SP00663 SP00664 SP00663 SP00664 SP00663 SP00664 SP00663 SP00664 SP00663 SP00663 SP00663 SP00663 SP00676 SP00736 SP00376 SP00376 SP00376 SP00376 SP00376 SP00376 SP00590 SP00590 SP00590 SP00590 SP00596	dddQ dddQ prpE acul naaR naaB naaB	DMSP lyase	[67]	-1.6	0.091
SPO0596 dakid DMSP lyses SPO0594 pript Activity-CoA lignee [63] 2.1 SPO0594 acard Activity-CoA lignee [70] 3.0 SPO0669 mand Activity-CoA legace [70] 3.0 SPO0669 mand Activity-CoA registration [70] 1.0 SPO0660 mand Acceptifuration ABC transporter, permanee [70] 1.0 SPO0663 mand Acceptifuration ABC transporter, ATP-binding [70] 1.1 SPO0663 mand Acceptifuration ABC transporter, ATP-binding [70] 1.1 SPO0675 mand Acceptifuration ABC transporter, ATP-binding [70] 1.1 SPO0675 mand Transmichalperone, peripherane [70] 1.1 SPO0675 le	SPO1596 SPO2934 SPO2934 SPO0659 SPO0660 SPO0660 SPO0662 SPO0663 SPO0663 SPO0663 SPO0663 SPO0664 SPO0663 SPO0664 SPO0663 SPO0664 SPO0668 SPO0676 SPO0376 SPO0376 SPO0376 SPO0376 SPO0376 SPO0376 SPO0590	dddQ prpE acul naaR naaB naaB	DMSP lyase	[88]	1.7	0.312
SPO0594 pmpR Averylander, On Higgase [63] 2.1 SPO0191 arad Arrylah CoA rehotates [70] 3.0 SPO0160 nand Transcriptional regulator [70] 1.3 SPO0661 nand Nacecyltamine ABC transporter, principles [70] 1.0 SPO0662 nand Nacecyltamine ABC transporter, principles [70] 1.0 SPO0663 nand Nacecyltamine ABC transporter, ATP binding [70] 1.0 SPO0663 nand Nacecyltamine ABC transporter, ATP binding [70] 1.1 SPO0663 nand Transine ABC transporter, ATP binding [70] 1.1 SPO0674 nand Transine ABC transporter, ATP binding [70] 1.1 SPO0675 nand Transine ABC transporter, ATP binding [70] 1.1 SPO0676 nand Transine ABC transporter, Def [71] 1.3 SPO0677 nand Transiciplicanine TRAP transporter, Def [71] 1.1 SPO0678 leeA Intermine Epytrapa except minime manne	SP02934 SP01914 SP01659 SP00666 SP00666 SP00666 SP00663 SP00663 SP00667 SP00667 SP00675 SP00675 SP00676 SP02356 SP02356 SP02356 SP02356 SP02356 SP03561 SP03561 SP03561 SP00592 SP00593 SP00599 SP00599 SP00595	prpE acul naaR naaA naaB	DMSP lyase	[69]	1.1	0.724
SPO 1914 aculd Acry loy-LCoA reductase [47] 15.0 SPO0660 num8 Transcriptional regulator 701 3.0 1.8 SPO0660 num8 N-accy lumine APC transporter, permease [30] 1.1 SPO0661 num8 N-accy lumine APC transporter, ATP-brinding [30] 1.1 SPO0662 num8 N-accy lumine APC transporter, ATP-brinding [30] 1.1 SPO0663 num6 N-accy lumine APC transporter, ATP-brinding [30] 1.1 SPO0673 num6 N-accy lumine APC transporter, ATP-brinding [30] 1.1 SPO0674 num4 Transic APC transporter, ATP-brinding [30] 1.1 SPO0675 num4 Transic APC transporter, ATP-brinding [31] 1.4 SPO0676 num4 Transcriptional Regulator [31] 1.2 SPO0675 num4 Transcriptional Regulator [32] 1.2 SPO0575 neck Inchinoma TRAP transporter, DrAM [32] 1.2 SPO0671 neck Inchinoma TRAP	SPO1914 SPO0669 SPO0660 SPO0661 SPO0663 SPO0663 SPO0664 SPO0663 SPO0664 SPO0664 SPO0667 SPO0674 SPO0674 SPO0586 SPO2356 SPO2356 SPO2356 SPO2356 SPO0673 SPO0673 SPO0673 SPO0673 SPO0673 SPO0679 SPO0699	acul naaR naaA naaB'	Acrylate-CoA ligase	[63]	2.1	0.225
SPO0060 naud8 Transcriptional regulator FOID 3.0 SPO0060 naud8 N-acetylaurine ABC transporter, pertubasnic FOI 1.8 SPO0060 naud8 N-acetylaurine ABC transporter, perturence FOI 1.2 SPO0064 naud7 N-acetylaurine ABC transporter, ATP-brinding FOI 1.1 SPO0064 naud7 N-acetylaurine ABC transporter, ATP-brinding FOI 1.1 SPO0064 naud7 N-acetylaurine ABC transporter, ATP-brinding FOI 1.1 SPO0063 naud8 N-acetylaurine ABC transporter, ATP-brinding FOI 1.1 SPO0063 naud8 Transcriptional regulator FOI 1.1 SPO0063 naud8 Transcriptional regulator FOI 1.1 SPO0185 riceA Icethionian TRAP transporter, DeAM FOI 1.2 SPO0186 riceA Icethionian TRAP transporter, DeAM FOI 1.2 SPO0186 riceA Icethionian TRAP transporter, and promessed FOI 1.2 SPO0186 riceA Ice	SPO0669 SPO0661 SPO0662 SPO0663 SPO0663 SPO0664 SPO0664 SPO0674 SPO0674 SPO0674 SPO0776 SPO2356 SPO2356 SPO2356 SPO2356 SPO0673 SPO0673 SPO0673 SPO0673 SPO0673 SPO0673 SPO0673 SPO0679 SPO0690	naaR naaA naaB	Acryloyl-CoA reductase	[47]	15.0	<0.001
Transport SPOOKS60 nauk Transcriptional regulator 70 3.0 Freedrich (STOK) 600 Nacceylamine ABC transports, promose 301 1.8 SPOOK62 nauß Nacceylamine ABC transports, promose 301 1.0 SPOOK63 nauß Nacceylamine ABC transports, ATP-blunding 301 1.0 stronk nauß Transic ABC transports, ATP-blunding 301 1.0 stronk nauß Transic ABC transports, ATP-blunding 301 1.0 stronk nauß Transic ABC transports, ATP-blunding 301 1.1 stronk nauß Transic ABC transports, ATP-blunding 301 1.1 stronk nauß	stransport SPO0669 stransport SPO0661 spo0662 SPO0663 spo0664 SPO0664 spo0664 SPO0667 spo0678 SPO0678 spo07 SPO0678 spo07 SPO0678 spo07 SPO0675 spo07 SPO0675 spo07 SPO0676 spo07 SPO07 sylaurine metabolism SPO0590 rt SPO0591 spo0592 SPO0590 spo0596 SPO0590	naaR naaB naaB'				
tumbolism Nacedylamin ABC transporte, pertiasent [30] 1.B tumbolism Nacedylamin ABC transporte, pertiasent [30] 1.D SPO0563 nund Nacedylamin ABC transporte, pertiasent [30] 1.D SPO0663 nund Nacedylamin ABC transporte, pertiasent [30] 1.D SPO0664 nund Nacedylamin ABC transporte, pertiasent [30] 1.D are Nacedylamin ABC transporte, ATP-bluding [30] 1.D are Nacedylamin ABC transporte, ATP-bluding [30] 1.B are Tumin ABC transporte, profiles [31] 1.B are Tumin ABC transporte, profiles [31] 1.B are Tumin ABC transporte, profiles [31] 1.B are Tumin ABC transporter, profiles [31] 1.B are Tumin ABC transporter, profiles [31] 1.B are Internacional Reparter, profiles [31] 1.B are Internacional Reparter, profiles [31] 4.B are Internacional	transport SPO0660	naaA naaB naaB'	Transcriptional regulator	[70]	3.0	0.008
SPOOK64 nand Avaccylamire ARC transports, permased 10 10 SPOOK63 nand Avaccylamire ARC transports, permased 190 1.2 SPOOK64 nand Avaccylamire ARC transports, ATP-binding 190 1.5 ort SPOOK65 nand Avaccylamire ARC transports, ATP-binding 190 1.1 ort SPOOK67 nand Tunnie ARC transports, ATP-binding 191 1.4 ort SPOOK67 nand Tunnie ARC transports, DebM 191 1.4 sport SPOOK67 nand Tunnie ARC transports, DebM 191 1.8 sport SPOOK67 nand Tunnie ARC transports, DebM 191 1.8 sport SPOOK67 nack Tunnie ARC transports, DebM 191 1.8 sport SPOOK67 nack Inchiname TRAP transports, perplanent 191 1.4 sport SPOOK67 nack Inchiname TRAP transports, perplanent 191 1.1 sport SPOOK68 nack Inchiname TRAP transp	SPO0661 SPO0662 SPO0663 SPO0663 SPO0664 SPO0665 SPO0676 SPO0675 SPO0675 SPO0675 SPO0676 SPO2356 SPO0356 SPO2356 SPO2356 SPO2358 SPO3561 SPO3561 SPO3561 SPO3561 SPO0590 TT SPO0599 Ism SPO0599 SPO0599 Ism SPO0599 Ism SPO0596 SPO0599 Ism SPO0596 SPO	naaB naaB'	N-acetyltaurine ABC transporter, periplasmic	[30]	1.8	0.118
SPOOK64 ninally Nacceptuarine ARC transports, Partnesse 300 1.2 remaibelism SPOOK64 ninal Nacceptuarine ARC transports, ATP-binding 300 1.5 stream SPOOK64 ninal Nacceptuarine ARC transports, ATP-binding 301 1.6 ort SPOOK65 ninal Transic plots and transports, ATP-binding 301 1.6 stream SPOOK65 ninal Transic plots and transports, ATP-binding 311 1.4 stream SPOOK67 ninal Transic plots and regulator portal 311 1.8 stream SPOOK67 ninal Transcriptional regulator portal 321 1.8 stream SPOOK67 ninal Transcriptional regulator 321 1.8 stream SPOOK67 ninal Transcriptional regulator 321 1.8 stream Section of the Interpreted an Action of the Interpreted and transporter, perplasment and transporter 321 1.2 stream Section of the Interpreted and transporter, perplasment and transporter 321 4.6	spoodes spoodes <td< td=""><td>naaB'</td><td>N-acetyltaurine ABC transporter, permease</td><td>[30]</td><td>1.0</td><td>0.920</td></td<>	naaB'	N-acetyltaurine ABC transporter, permease	[30]	1.0	0.920
SPOX663 nuac N-accyluturine ARC transporte, ATP-binding [50] 1.5 rencholism SPOX654 nuac N-accyluturine ARC transporte, ATP-binding [50] 1.1 art N-accyluturine ARC transporte, portlydene [50] 1.6 1.1 art SPOX653 nuac Transin-bydrohase [50] 1.6 1.1 art SPOX654 nuac Transin-bydrohase [51] 1.8 1.1 sport SPOX655 nuac Transin-bydrohase [51] 1.8 1.8 sport SPOX155 nuac Transcriptional regulator [51] 1.8 1.8 sport SPOX155 nucl Inchinate TRAP transporter, cond [52] 1.8 1.2 sport SPOX155 nucl Inchinate TRAP transporter, cond [52] 1.8 1.2 sport SPOX155 nucl Inchinate TRAP transporter, cond [52] 1.2 2.0 sport SPOX155 nual Transcriptional regulator [53]	rmetabolism SP00663 rmetabolism SP00657 sort SP00658 sort SP00674 spoot SP00675 spoot SP02355 spoot SP02356 sp02357 SP02356 sp02357 SP02356 sp02357 SP02359 sp02357 SP02359 sp02356 SP02359 rt SP03561 sp03561 SP03561 sp03561 SP03561 sp03561 SP03561 sp03561 SP03561 sp03561 SP03561 sp03561 SP03561 sp03562 SP03561 sp03562 SP03561 sp03562 SP03562 sp03662 SP0356		N-acetyltaurine ABC transporter, permease	[30]	1.2	0.700
SPO0564 mack Neacelylaarine ABC transporter, ATP-binding 150 115 rinetabolism SPO0687 mack Neacelylaarine ABC transporter, Periplesmite 130 1.1 rint Neacelylaarine and ABC transporter, periplesmite 331 1.4 1.4 strat Neacelylaarine and ABC transporter, periplesmite 331 1.4 1.4 strat Taurine ABC transporter, periplesmite 331 1.4 1.3 strat Taurine ABC transporter, periplesmite 331 1.8 1.8 strat Transcriptional regulator 321 1.8 1.8 strat Lecthorane TRAP transporter, periplesmite 321 1.8 1.8 strat Besthiname TRAP transporter, periplesmite 321 1.8 1.8 strat Lecthorane TRAP transporter, periplesmite 321 1.8 1.8 strat Intenscriptional regulator 321 1.8 1.8 strat Strategional regulator 321 4.6 1.7 strat Problema accyltransferase	rmetabolism SP00664 sort SP00657 spr00674 SP00674 spr00675 SP00676 spr00676 SP02355 spr02355 SP02355 spr02356 SP02356 spr02357 SP02357 spr02357 SP02359 spr02358 SP005350 rt SP005361 spr03561 SP00530 rt SP00591 spr00592 SP00593 sism SP00595 spr00596 SP00596 spr00596 SP00596	naaC	N-acetyltaurine ABC transporter, ATP-binding	[30]	1.5	0.371
rencholism SPOOK54 nund Metallochapterone, putative [30] 1-11 ort SPOOK54 munh Turnien AbC transporter, ATP-binding [31] 1.6 ort SPOOK54 munh Turnien AbC transporter, ATP-binding [31] 1.8 sport SPOOK55 muh Transporter, permasse [31] 1.8 sport SPOOK56 isch Transporter, permasse [31] 1.8 sport SPOOX55 isch Rethioante TRAP transporter, DeAM [32] 1.25 sport SPOOX55 isch Rethioante TRAP transporter, periphasmic [32] 2.03 shoulinen metabolism SPOOX55 isch Rethioante delydrogenase [31] 5.7 shuimine/sethioante metabolism SPOOX55 muk Transcriptional regulant [31] 4.6 shuimine/sethioante metabolism SPOOX56 muk Transcriptional regulant [31] 1.7 strongssyst ing Phydroxyperquestificante ceryltransferase [31] 1.7	retabolism SP00657 retabolism SP00658 SP00675 SP00675 SP00675 SP00675 SP00355 SP00355 SP00356 SP02358 SP02358 SP02358 SP02358 SP02359 rt SP00591 SP00591 SP00591 SP00592 SP00595 SP00595 SP00595 SP00595 SP00595 SP00596 SP00596 SP00596 SP00596 SP00596 SP00596 SP00596 SP00596 SP00596 SP00599 SP00596 SP005	naaC'	N-acetyltaurine ABC transporter, ATP-binding	[30]	1.9	0.108
9TOMOSA Named Name Number Obstancine annidoly drobuse 39 1.6 9TOMOSA tand Namire ABC transporter, periplasmic 31 1.4 8POMOSA tand Taunire ABC transporter, periplasmic 31 1.3 8POMOSA tang Taunire ABC transporter, permease 31 1.3 8port SPOMOSA tack Isethioant TRAP transporter, permease 32 1.8 8port SPOMOSA tack Isethioant TRAP transporter, permease 32 6.2 about SPOMOSA tack Isethioant TRAP transporter, periplasmic 32 1.8 about Transcriptional regulator 32 2.2 6.2 ylumine/isethionate metabolism SPOMOSA tang Transcriptional regulator 31 4.6 ylumine/isethionate metabolism SPOMOSA tag Transcriptional regulator 31 4.6 ylumine/isethionate metabolism SPOMOSA tag Transcriptional regulator 31 4.6 promosa promosa promosa promosa	SPO0658 SPO0674 SPO0675 SPO0676 SPO0676 SPO0676 SPO0355 SPO0356 SPO03358 SPO03358 SPO03358 SPO03358 SPO03358 SPO03358 SPO0350 T SPO0590 T SPO0590	naaT	Metallochaperone, putative	[30]	-1.1	0.878
out Tunnir ABC transporter, Periplisantic 311 1.4 SPONGYS nunB Tunnir ABC transporter, Periplisantic 311 1.4 SPOGYS nunB Tunnic ABC transporter, permease 321 1.8 SPOGYSS ised Transcriptional regulator 322 1.8 sport SPOGASS ised Tennscriptional regulator 322 1.8 sport SPOGASS ised Lectionane TRAP transporter, periplisantic 322 1.8 abolism SPOGASS ised Lectionane TRAP transporter, periplisantic 321 1.8 abolism SPOGASS ised Destinoane delydogenase 321 1.8 abolism Propabate accyltransferase 311 1.17 1.17 ylumine/sethionate metabolism SPOGSS pin Disposabate accyltransferase 311 1.13 state SPOGSS pin Disposabate accyltransferase 311 1.17 state SPOGSS pin Disposabate accyltransferase 311 1.17	SP00674	naaS	N-acetyltaurine amidohydrolase	[30]	1.6	0.239
SPO0675 nutB Tautine ABC transporter, ATP-binding [31] 1.3 sport SPO3676 inc Taunine ABC transporter, permease [31] 1.3 sport SPO3575 inck Lecthionaue TRAP transporter, portplasmic [32] 1.25 sport SPO3576 inck Inchionaue TRAP transporter, periplasmic [32] 1.25 shobism SPO3578 inck Inchionaue TRAP transporter, periplasmic [32] 1.84 shobism SPO3579 inck Inchionate TRAP transporter, periplasmic [32] 1.84 shobism SPO3562 inck Inchionate TRAP transporter, periplasmic [32] 1.84 shobism SPO3562 inck Transcriptional regulator [31] 4.6 shuth SPO3563 inck Sulfoacetaldebyde acetyltransferase [31] 1.17 stront SPO3560 input Transcriptional regulator [28] -6.3 stront SPO3591 input Dhydroxyproparaculforane Graph Transporter [28] -2.84	sport SP00675 sport SP02355 sport SP02356 spo2357 SP02356 spo2358 SP02356 spo2357 SP02356 spo2358 SP03562 spo2356 SP03561 spo23561 SP03561 spo3561 SP03561 spo3562 SP03561 spo3562 SP03561 spo3562 SP03561 spo3562 SP03561 spo3562 SP03561 spo3562 SP03562 spo3562 SP03562 spo3562 SP03562 spo3662 SP03562 spo3662 SP	tauA	Taurine ABC transporter, periplasmic	[31]	1.4	0.423
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SPO0596 hpsP S- or R-DHPs-2-dehydrogenase [28] -40.2 SPO0598 s/cD Sulfolactate dehydrogenase [28] -21.4 SPOA0159 cuyR Transcriptional regulator [28] 1.2		Osdy	R- or S-DHPS-2-dehydrogenase	[28]	-28.9	<0.001
SPO0598 s/cD Sulfolactate dehydrogenase [28] -21.4 SPOA0159 cayR Transcriptional regulator [28] 1.2		Asdu	S- or R-DHPS-2-dehydrogenase	[28]	-40.2	<0.001
SPOA0159 cuyR Transcriptional regulator [28] 1.2		slcD	Sulfolactate dehydrogenase	[28]	-21.4	<0.001
	SPOA0159	cuyR	Transcriptional regulator	[28]	1.2	0.70

Adjusted p value 0.039 0.065 < 0.001 <0.001 20.00 Differential expression results Fold difference -3.0 4. 9.0 6.3 2.7 -3.1 This study This study This study This study Reference [58] [35] [35] [35] [35] [35] Glycine betaine:homocysteine methyltransferase Betaine-aldehyde dehydrogenase Dimethylglycine dehydrogenase ABC transporter, ATP-binding ABC transporter, periplasmic ABC transporter, permease ABC transporter, permease Sarcosine dehydrogenase Choline dehydrogenase .-Cysteate sulfolyase -cysteate sulfolyase Choline sulfatase cuyAbetA betB SPOA0158 Locus tag SPO2657 SPO2659 SPO1083 SP03400 SP02660 SPO1088 SPO0084 SP03398 SP03396 SP02658 SP02661 Choline-O-sulfate metabolism Choline-O-sulfate utilization Fable 1 (continued) Cysteate metabolism Choline metabolism Cysteate transport DHPS metabolism vsteate utilization

Positive fold differences indicate genes with higher relative expression during the dinoflagellate-dominated phase; negative fold differences represent genes with higher relative expression during the diatom-dominated phase. Numbers in bold indicate statistical significance. Experimental verification of gene function in R. pomeroyi is indicated in the Reference column. the higher expression of *R. pomeroyi* C2 sulfonate genes during the dinoflagellate phase suggests greater release by the dinoflagellate than by the diatom. *N*-acetyltaurine has not yet been identified in phytoplankton metabolomes.

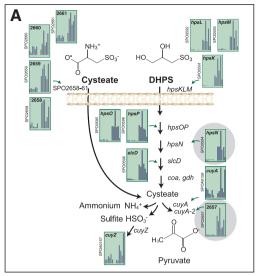
Sulfate ester metabolism

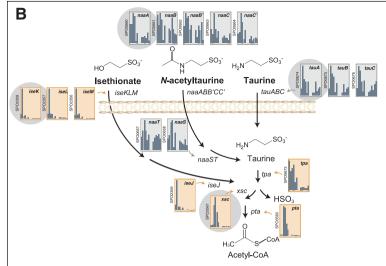
We noted enrichment of transcripts from *betC* (choline sulfatase) and *betI* (choline catabolism transcriptional regulator) during growth of *R. pomeroyi* on dinoflagellate-derived metabolites. *betC* was previously experimentally verified as an essential gene in the catabolism of the sulfate ester choline-O-sulfate by *R. pomeroyi* [35]. Transcription analysis of the bacterium growing on choline-O-sulfate compared to acetate identified *betC* and *betI* among the most highly enriched, along with transcripts from several downstream genes that process choline to glycine betaine, sarcosine, and glycine (Fig. 2c and Fig. S2). This DOS metabolite was previously identified in the metabolome of dinoflagellate *Amphidinium carteri* [36, 37].

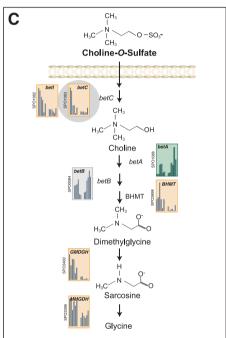
Sulfonium metabolism

Ruegeria pomeroyi harbors two degradation pathways for the sulfonium compound DMSP, each with different physiological and ecological fates. DMSP-sulfur processed through the demethylation pathway is incorporated into cellular material or oxidized for energy, while DMSP-sulfur processed through the cleavage pathway is largely lost from the cells in the form of DMS [38] (Fig. 2d). In the axenic controls, dissolved DMSP accumulated to $1050 \pm 117 \text{ nM}$ (Fig. 1e), while in the R. pomeroyi co-cultures accumulation was only 1.4 ± 0.4 nM, indicative of highly efficient bacterial uptake. Transcription of the first genes in each of the pathways (dmdA for demethylation, dddW for cleavage) was significantly higher during the dinoflagellate phase (Table 1). This is consistent with previous data showing that although T. pseudonana also synthesizes DMSP, A. tamarense is the higher producer of the two [39]. We checked whether this was the case under the specific growth conditions used here and found 772 ± 3 nM DMSP in the A. tamarense exometabolome vs. $101 \pm 18 \text{ nM}$ in the T. pseudonana exometabolome after 1 week of axenic growth. Although R. pomeroyi has other genes that can also mediate the first step in the DMSP cleavage pathway [dddD, dddP, dddQ [40]], only dddW was expressed to any appreciable levels.

The timing of peak expression of the gatekeeper genes for demethylation (*dmdA*) vs. cleavage (*dddW*) was offset in the co-culture by 3–5 days (Fig. S3). Variations in the ratio of DMSP routed through the two pathways have been detected in natural marine bacterial communities as well [8, 41], although the controls over this differential routing







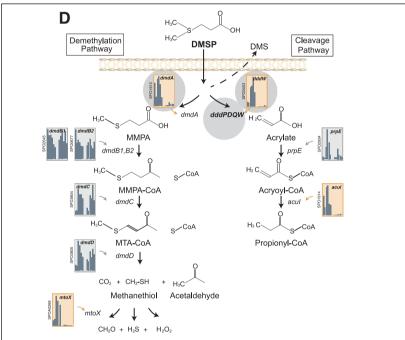


Fig. 2 Expression of organic sulfur pathways by *R. pomeroyi*. Histograms indicate relative expression (TPM) for genes encoding transformation of a C3 sulfonates, b C2 sulfonates, c a sulfate ester, and d a sulfonium compound. The first six bars in each represent expression during the dinoflagellate phase (sampling days 7, 9, and 12) and the last six bars represent expression during the diatom phase (sampling

days 23, 30, and 37), with replicates (n=2) shown separately. Orange backgrounds indicate genes with significant enrichment in the dinoflagellate phase and green indicate significant enrichment in the diatom phase (DESeq2, p < 0.05). Genes used in the Tara Oceans bioinformatic analysis are marked with gray circles

are still not understood [42]. Because DMSP demethylation produces hydrogen peroxide [43–45] and cleavage produces acrylate/acryloyl-CoA [46, 47], one hypothesis views differential regulation as a mechanism for bacteria to balance the different physiological stresses each pathway imposes [48]. In the co-culture experiment, expression of the R. pomeroyi catalase gene (katG) was significantly correlated with expression of demethylation pathway genes (dmdA and mtoX; r = 0.73 and 0.89, $p \le 0.01$), but not with the

cleavage pathway gene dddW (r = 0.27; Fig. S3), consistent with hydrogen peroxide stress linked to demethylation. Acryloyl-CoA reductase (acuI) from the cleavage pathway is co-located and co-regulated with dmdA from the demethylation pathway (Fig. S3), an unusual arrangement that, upon upregulation of the operon, would protect the bacterium both by metabolizing acryloyl-CoA generated in the cleavage pathway and routing DMSP into the demethylation pathway. We checked whether acryloyl-CoA

accumulation switches gene expression to the demethylation pathway by adding acrylate, the precursor of acryloyl-CoA, to *R. pomeroyi* cultures growing on DMSP. As hypothesized from the genome organization, the relative DMSP flux through demethylation pathway increased significantly upon acrylate addition (Fig. S4).

Sulfur fate in Ruegeria pomeroyi

The S moiety in sulfonates is more oxidized than in DMSP and therefore less valuable as a reduced sulfur source for bacterial biosynthesis. For the inorganic sulfur derived from the three dinoflagellate-derived sulfonates (taurine, N-acetyltaurine, and isethionate), sulfur has been shown to be exported from R. pomeroyi via the soe system in the form of sulfate [49, 50]. Consistent with this, there was higher average expression of soeABC during the dinoflagellate phase, and expression of soe genes had significant positive correlations with tauR, xsc, and pta (Fig. S5). Inorganic sulfur from the two C3 diatom-derived sulfonates (DHPS and cysteate) is exported by R. pomeroyi instead in the form of sulfite via the cuyZ gene [28, 51]. cuyZ had peak expression in the diatom phase (Fig. S5). Finally, inorganic sulfur from DMSP metabolism is exported by R. pomeroyi in the form of sulfate using a third system, soxABCDXYZ [52]. Expression of sox genes peaked during the dinoflagellate phase and was significantly correlated with expression of DMSP demethylation gene dmdA (Fig. S5).

DOS transformation by ocean bacteria

We used knowledge of the sulfur metabolites important in this model system to characterize the capacity for DOS utilization by ocean bacteria. Thirteen bacterial genes indicative of catabolism of phytoplankton-derived organic sulfur molecules were analyzed in the Tara Oceans metagenomic database [16]. DNA sequences representing the bacterial/archaeal size class of marine plankton (0.22-1.6 or 0.22-3 µm filter pore-size ranges; Table S3) from surface (100 samples from 5 m depth), DCM (72 samples from 17 to 188 m depths), and mesopelagic (53 samples from 250-1000 m depths) collections (Fig. S6) were assembled into contigs by individual sample (see Methods), which allowed us to link reads back to the station and depth where they were collected. HMM searches were conducted for genes characteristic of the model system sulfur metabolites, using diagnostic catabolic genes or, in the case of the C2 sulfonates that share catabolic genes, using transporter binding proteins (Fig. 2). The percent of genomes harboring the genes was estimated based on length-normalized ratios to recA, a housekeeping gene present in single copy in all bacterial and archaeal genomes. The sum of recA sequences across all samples (Table S3) indicated that 1.4 million bacterial/archaeal genome equivalents were surveyed in these Tara Oceans collections, of which ~650,000 were from the surface ocean, ~500,000 from the DCM, and ~230,000 from the mesopelagic.

The frequency of genes for DOS utilization averaged across all locations and depths is highest for DMSP, and this is the only DOS metabolism capability identified in all 225 Tara samples. Twenty percent of bacterial genomes harbored dmdA, the diagnostic gene for DMSP demethylation, while 3.8%, 2.5%, and 2.4% of genomes had dddK, dddP, and dddD, the most abundant DMSP cleavage genes (Table S3). Although dddW was the most highly transcribed of the R. pomeroyi DMSP cleavage genes in the co-culture, it is extremely rare in the Tara dataset—present in only 92 of the 1.4 million genome equivalents we surveyed (0.01% of genomes; Table S3). Cleavage genes dddL and dddQ were found in 0.06% and 2.3% of genomes; whether DMSP cleavage is the native function of dddQ has been questioned [53]. A recent analysis of DMSP cleavage gene expression in the Tara Oceans metatranscriptome data shows they are actively expressed, with dddP and dddK having the highest transcription levels [54].

Genes for utilization of sulfoacetaldehyde (xsc), taurine (tauA), and DHPS (hpsN) are the next most frequent in Tara bacterioplankton (estimated to be in 8.4%, 8.2%, 4.8% of genomes). Genes for transforming choline-O-sulfate (betC) and isethionate (iseK) are not frequent (0.9% and 0.5% of genomes) (Table S3). Notably, bacterial DOS genes are not distributed evenly by depth. DMSP demethylation gene dmdA and cleavage gene dddK had distributions significantly biased toward surface ocean bacterial genomes. The DMSP cleavage gene dddP and genes for taurine (tauA), N-acetyltaurine (naaA), cysteate (cuyA-2), isethionate (iseK), and sulfoacetaldehyde (xsc) utilization had distributions significantly biased toward mesopelagic bacterial genomes (Fig. 3).

To learn which bacterial taxa harbor DOS genes, we assigned taxonomy to the Tara genes based on blast analysis against the Integrated Microbial Genomes non-redundant database. For all DOS genes except dddK, taxonomic assignments include bacteria belonging to the Rhodobacterales, an expected consequence of Rhodobacterales member R. pomeroyi being the sensor bacterium that generated the DOS metabolite list. Because of the numerical importance of SAR11 cells in the ocean, they dominate the taxonomic assignments for any DOS genes found in the group. Thus, SAR11 genomes account for >80% of bacterial genes for DMSP utilization (dmdA and dddK), >55% of genes for DHPS utilization (hpsN), and >60% of genes for taurine utilization (tauA). Other marine Alphaproteobacteria from the SAR116, Rhodospirillales, and Rhizobacterales clades also harbor DOS genes, but to a lesser extent than Rhodobacterales and SAR11 (Fig. 4).

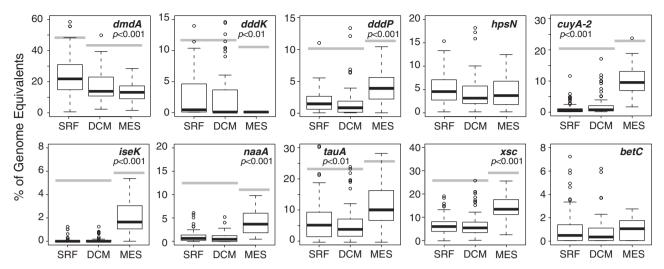


Fig. 3 Dissolved organic sulfur (DOS) metabolite genes in the ocean. Relative abundance of 10 DOS metabolite genes in marine bacterial/ archaeal genomes was estimated by normalizing to *recA* counts for 100 surface, 72 deep chlorophyll maximum (DCM), and 58 mesopelagic samples from the Tara Oceans database. For genes with

significant differences in relative abundance by depth zone (analysis of variance (ANOVA)), gray bars connect zones that are not statistically different (Tukey's honestly significant difference (HSD) multiple comparison)

In the mesopelagic, novel groups not previously recognized for organic sulfur metabolism were prominent (Fig. 4). One such group is SAR324, whose genomes contain orthologs for utilization of DMSP (dmdA and dddP), DHPS (hpsN), taurine (tauA), N-acetyltaurine (naaA), isethionate (iseK), and choline-O-sulfate (betC). For example, SAR324 genomes account for 41% of dmdA, 92% of iseK, and 29% of tauA in bacteria sampled from mesopelagic depths. A second novel taxon potentially participating in DOS metabolite catabolism at depth is the Acidimicrobiia group of the Actinobacteria, whose genomes contain orthologs for utilization of N-acetyltaurine (30% of mesopelagic *naaA*), taurine (1% of mesopelagic tauA), and DMSP cleavage (46% of mesopelagic dddP). The Acidimicrobiia tauA and naaA genes in the Tara data are uncharacteristically long (~680 amino acids compared to ~300 in other bacteria), which was due to two substrate binding domains encoded in each. Two substrate binding domains were also found in tauA and naaA in some marine Acidimicrobiia reference genomes (Fig. 5), an arrangement that could improve scavenging for scarce substrates. A third novel group at DCM and mesopelagic depths is *Thioglobus*/ SUP05, whose genomes contain orthologs for DMSP cleavage (21% of DCM dddP, 7% of mesopelagic dddP) and taurine utilization (11% of DCM tauA, 33% of mesopelagic tauA). Lastly, DOS genes that mapped to a novel Gammaproteobacteria group with 16S rRNA sequences most similar to Thiohalorhabdaceae bacterium JGI 01 F9 750m (95% identity) included those for DMSP demethylation (13% of mesopelagic dmdA) and N-acetyltaurine utilization (51% of mesopelagic *naaA*) (Fig. 4).

Two catabolism genes used in the Tara HMM searches, cuyA-2 and xsc, are not specific for a single DOS metabolite. cuyA-2 encodes a second copy of L-cysteate sulfolyase for cysteate metabolism in R. pomeroyi (Fig. 2a), but might not be distinguishable from the canonical cuyA from the DHPS pathway in homology-based searches. xsc encodes a sulfoacetaldehyde acetyltransferase that in R. pomeroyi mediates a step in the shared lower pathway through which C2 sulfonates taurine, N-acetyltaurine, and isethionate are degraded (Fig. 2b), but this gene is also used in an alternate pathway for DHPS catabolism by some marine bacteria [28]. Taxonomic assignments of cuyA-2 and xsc are dominated by SAR11, Rhodobacter, SAR324, and Gammaproteobacteria, and their frequency and distribution are consistent with other sulfonate utilization genes (Table S3).

In cases where HMMs identified orthologs in taxa not previously recognized to transform DOS, we carried out synteny-based checks on the annotations by examining gene neighborhoods in the Tara assemblies and in their closest reference genomes. The co-location of genes with annotations consistent with DOS metabolism corroborated the HMM annotations (Fig. 5). The HMMs did not recover any orthologs originating from archaeal genomes, although we note that there were no characterized marine archaeal DOS genes to include in the HMM reference sequences.

Insights into DOS processing and fate

Bacteria capable of DMSP utilization are the most frequent DOS degraders in the Tara Oceans database, an expected result given both that ~10% of marine net primary

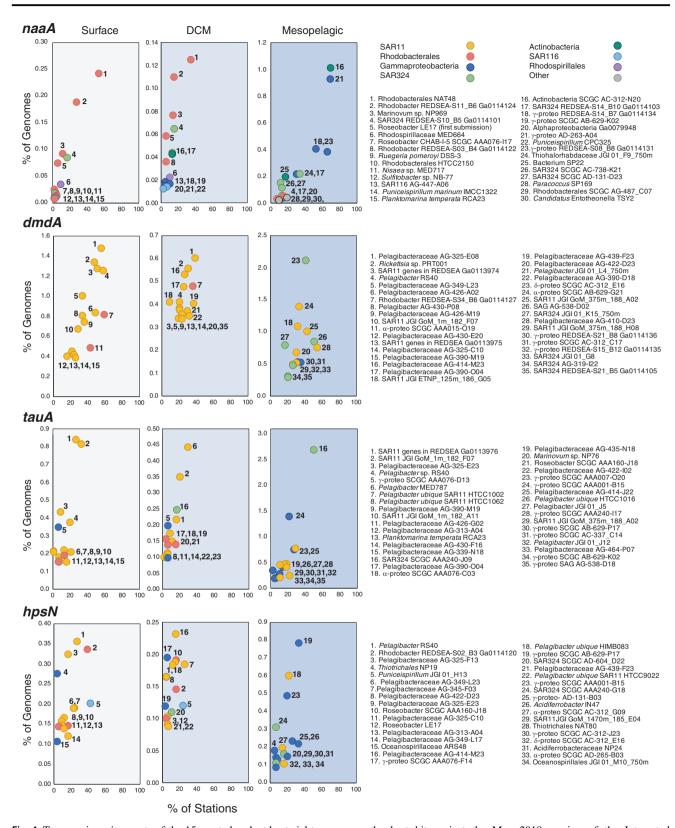
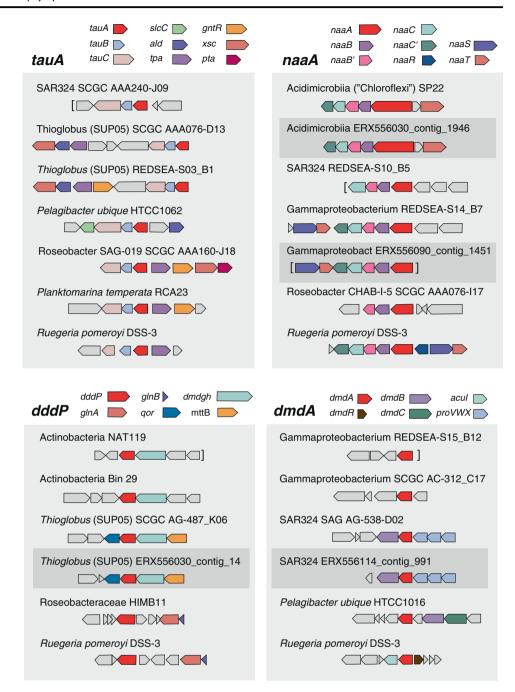


Fig. 4 Taxonomic assignments of the 15 most abundant bacterial taxa at each depth zone harboring DOS metabolite genes *naaA*, *dmdA*, *tauA*, and *hpsN*. Taxonomy was obtained for Tara Oceans genes based

on the best hit against the May 2018 version of the Integrated Microbial Genomes non-redundant database

Fig. 5 Gene neighborhoods of dissolved organic sulfur (DOS) metabolite genes in Tara Oceans contigs (dark gray shading, ERX556xxx labels), the closest reference sequences to these genes, and model bacterium *R. pomeroyi. tauA*, taurine transport; *naaA*, *N*-acetyltaurine transport; *dddP*, DMSP cleavage; *dmdA*, DMSP demethylation. Genes colored gray are unrelated to organic sulfur metabolism. Brackets indicate contig ends



production is directed to DMSP synthesis [8, 55] and phytoplankton intracellular concentrations can reach 400 mM [39, 56]. Marine bacteria serving as model organisms for DMSP gene discovery, including *R. pomeroyi*, can harbor up to four different DMSP cleavage genes in addition to *dmdA* [40, 42]. Yet, based on the frequency of cleavage genes in the Tara dataset compared to demethylation gene *dmdA*, it appears that most oceanic DMSP-degrading bacteria are capable only of demethylation. Among DMSP-degrading SAR11 cells, for example, frequencies of *dmdA* and *dddK* indicate that no more than 25% can harbor both pathways. Although community gene

frequency is not a measure of activity level, the lower frequency of cleavage genes accords with estimates that <2% of the DMSP synthesized by marine phytoplankton is ultimately released from the ocean surface as DMS [42]. Nonetheless, this small DMS flux relative to DMSP production accounts for over 40% of Earth's atmospheric sulfur burden [41], and even minor changes in bacterial routing between the two pathways could impact atmospheric sulfur concentrations.

The fact that DMSP genes *dmdA* and *dddK* have frequencies biased toward surface ocean genomes suggests a close coupling between phytoplankton synthesis and

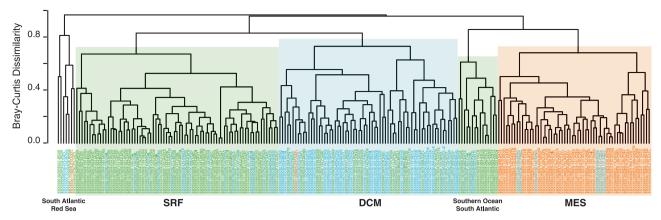


Fig. 6 Dendrogram of a Bray–Curtis dissimilarity matrix constructed from the relative abundance (as % of genome equivalents) of 10 dissolved organic sulfur (DOS) metabolite genes in 225 Tara Oceans bacterial/archaeal size fraction datasets (Table S3). Sample names are colored based on collection depth (green = surface; blue = DCM;

orange = mesopelagic) and indicate sample number ("ERX55xxxx"), followed by depth zone (XXX), station number (123), and the Tara Oceans biome code (XXXX). For two smaller clusters containing samples from mixed depths, the main ocean regions of origin are indicated

bacterial transformation for this compound. Yet, in the case of sulfonate genes, with frequencies mostly biased toward mesopelagic genomes, the proximate source of labile DOS is less clear. Sulfonate-sulfur is more oxidized than DMSPsulfur and may be less preferred as a substrate in surface waters. Sinking phytoplankton biomass could also provide a source of sulfonates at depth, as supported by evidence of DHPS production during bacterial degradation of sulfolipids from photosynthetic membranes [57]. DOS metabolites could also be available from viral lysates and zooplankton detritus. For example, taurolipids have been identified in protist membranes [58], and taurine release by crustacean zooplankton has been observed in surface and upper mesopelagic waters [59]. When the Tara Ocean samples are clustered based on gene patterns, collection depth is the main correlate (Fig. 6), with depth-related variation in both sources of DOS and the bacterial taxa that process DOS likely to be driving this pattern. Only minor groupings were observed based on oceanic region, although a separate cluster of 15 surface and DCM samples with high DOS gene abundance emerged, driven primarily by high frequencies of genomes with dddK, hpsN, and tauA (Fig. 6).

Our important findings are, first, that a diverse suite of DOS metabolites have the potential to support bacterial heterotrophy in the ocean. Membership in this suite may well expand further, particularly when viewed through a more comprehensive lens than just a single model bacterium's gene expression. The recent finding that the structurally unusual DOS compound dimethylsulfoxonium propionate is an exometabolite of marine phytoplankton and readily taken up by marine bacteria, including *R. pomeroyi* [60], supports this prediction. The biosynthetic apparatus and physiological roles of these DOS metabolites in marine phytoplankton remain largely unknown. Second, in addition to the bacterial taxa already

recognized to play roles in organic sulfur transformation (Rhodobacter, SAR11, and SAR116), we discovered that other taxonomic groups can process DOS metabolites and have gene frequencies biased toward the mesopelagic. These include SAR324, Acidimicrobiia, Thioglobus/ SUP05, and Thiohalorhabdaceae-like cells with varying capabilities for utilization of DMSP, taurine, N-acetyltaurine, isethionate, and choline-O-sulfate. Non-labile marine DOS (defined as the semi-polar molecules captured on solid-phase extraction resin) in the ocean's dissolved organic matter reservoir has been found to degrade at a higher long-term rate than bulk DOC, indicating selective removal of organic sulfur over time and depth [61]. Here, an analysis window targeting the labile components of marine DOS similarly implicates organic sulfur turnover as a key process in the global carbon cycle.

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Author contributions ML and MAM conceived of the study and wrote the paper with input from all authors. ML, ASB, BPD, KE, RPK, BN, and AV performed experiments or conducted analyses; TN and SS assembled and analyzed sequence data; ML, RPK, and MAM analyzed data and interpreted findings.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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