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Editorial: Applying metabolomics to questions in marine ecology and ecophysiology

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Editorial on the Research Topic
Applying metabolomics to questions in marine ecology and ecophysiology

High biodiversity and deep evolutionary histories have led to the extreme diversification of molecules in the ocean, explaining why some of humanity's most potent drugs have been discovered in marine organisms. Historical challenges in sampling and extracting molecules from marine life and seawater, along with the sparsity of molecular reference libraries, leaves much to be explored in the marine chemosphere (Steen et al.). With the ongoing global loss of marine biodiversity due to anthropogenic pressures (O'Hara et al., 2021), opportunities to identify new marine molecules are declining. Here, we identify advances in metabolomics that can rapidly generate new knowledge about the ecology and evolution of marine molecules, while aiding the pursuit of new drugs to fight emerging diseases.

Metabolomics offers a high sensitivity tool in the toolkit of ecologists

Apply database-adjacent and database-independent methods

Marine metabolomes often yield extremely low molecular identification rates (da Silva et al., 2015), routinely falling below 2% (e.g., Quinn et al., 2016; Hartmann et al., 2017). New chemi- and bioinformatic approaches can improve annotation rates beyond searching reference libraries, while others avoid reference libraries by

characterizing specific aspects of molecular structures. Bioinformatic approaches to improve the annotation of marine molecules include *in silico* structure prediction tools from tandem mass spectra, often based on fragmentation trees, such as SIRIUS and DeepEI (Dührkop et al., 2019; Ji et al., 2020, respectively). Despite these advances, high error rates and uncertainty of molecular predictions remain a challenge in the field.

Molecular networking of tandem mass spectrometry data groups structurally related molecules with putatively similar functions without the need for molecular identifications. These networks expand the frame of inference from changes in individual molecules to chemosphere-wide shifts in the marine environment over time (Petras et al., 2021a). Networking can also illuminate molecular modifications based on known mass shifts between related molecules (e.g., 2.016 Da = H_2). This approach has identified specific biochemistries activated in response to environmental change (Hartmann et al., 2017; Quinn et al., 2020; Petras et al., 2021b; Gamba et al., 2022). Li et al. took this approach a step further by combining hardware modifications and new data analysis algorithms to improve the quantification of trace metabolites in seawater and classify them with novel elemental mass search algorithms for bound nutrients. Their approach expands our understanding of a large group of ecologically important molecules in the sea, siderophores and other trace metal organic ligands produced by marine microalgae, without the need for complete structural elucidations.

Combine -omics

Multi-omics refers to approaches that combine -omics tools and datasets. While metabolomics provides a desired level of resolution—effector molecules—it rarely offers the full story due to the lack of molecular annotations. To identify the source of molecules and the environmental conditions that stimulate their production, it is necessary to connect molecules back to genes or organisms. These connections are being made with recent tools that use co-occurrence networks, machine learning, and neural networks (e.g., Sogin et al., 2017; Roach et al., 2020; Little et al., 2021). For example, mmvec (Morton et al., 2019), a neural network approach, was used to identify an association between a specific bacterial strain and two coral molecules, demonstrating specific links between the coral microbiome and its metabolome (Little et al., 2021).

Use metabolomics for hypothesis testing

The application of metabolomics to hypothesis testing is limited by inconsistent detection of target metabolites, the inaccuracy of quantifications, and the dearth of molecular annotations (Steen et al.). The approaches described above demonstrate that expanding analyses beyond known molecules to whole networks or shared chemical transformations (i.e., across many molecules) can smooth out single-molecule variation, increasing potential for hypothesis testing. As an example, networking was used to find hydration/dehydration reactions throughout mostly unknown molecules in coral holobionts and demonstrated that coral mitochondria and algal symbiont cells adjust membrane fluidity in opposite directions in response to elevated temperatures (Gamba et al., 2022).

Apply metabolomics across scales of biological and environmental organization

The fundamental role of molecules in carrying out physiological functions makes them useful across scales of biological organization. For example, sampling organelles and cells can be used to characterize biochemical pathways, sampling holobionts (as individuals and host species) can be used to profile the molecular phenotypes of individuals and species, and sampling communities and ecosystems can quantify the chemical diversity of entire systems. Applications of sampling at scales reveal that distinct organelles and cell types have disparate physiological responses to the same stimulus (Gamba et al., 2022), individual holobionts of the same host species have different molecular profiles (Sogin et al., 2016; Hartmann et al., 2017; Lohr et al., 2019), and holobionts of closely related host species show large differences in their molecular profiles and responses to stress (Quinn et al., 2016; Sweet et al., 2021).

The application of metabolomics is particularly powerful in microbiology. These tools can be used to identify the unique chemicals and ecophysiologies of bacteria, such as surprisingly high sugar production in the seagrass rhizosphere or the production of novel bile salts that aid digestion in the human gut (Quinn et al., 2020; Sogin et al., 2022, respectively). In marine ecology, metabolites mediate interactions between bacteria and between bacteria and metazoans (Hay, 2009). For example, chemical signals produced by surface-associated bacteria (e.g., on the seafloor) attract or deter invertebrate larvae and algal spores from settling (Hadfield and Paul, 2001). Settlement is often accompanied by metamorphosis to an adult stage, which in turn dictates local community composition, community succession, and biodiversity. The chemicals that attract or deter settlement can be leveraged for valuable applications including ecosystem restoration and the development of antifouling compounds. Advancements in mass spectrometry are being used to produce two-dimensional maps of metabolites across space, providing extremely highly resolved chemical landscapes and pinpointing new chemical signals with ecological functions (Watrous and Dorrestein, 2011).

Study extracellular metabolites in seawater to identify key physiological processes

Marine organisms release molecules into seawater for many reasons, including acquiring mutualistic symbionts, attracting or killing bacteria, defending against predators and competitors, and preying upon other organisms (Hay, 2009). The evolution of these behaviors and associated molecules is likely influenced by the predictable direction and protracted residence time of molecules in seawater in contrast to air. Few of these exometabolites, or molecules produced by organisms in the environment, have been characterized (summarized in Kelly et al., 2021). This dissolved organic matter can be extracted from seawater using solid phase extraction (SPE) columns (Dittmar et al., 2008) and analyzed using traditional tools, including approaches that overcome salt contamination (Sogin et al., 2019). Sampling the exometabolome is particularly informative because it isolates the molecules that holobionts release in response to changes in their environment, rather than all the molecules in the holobiont's tissues. Isolating the exometabolome thus allows researchers to identify molecular indicators of the stress or the molecules acting against it (e.g., antibacterial compounds), focusing data outputs on those most relevant to the ecological interaction being studied (Roach et al., 2020; Kelly et al., 2021). As an example, riboflavin was enriched in benthic seawater across numerous reefs relative to surface seawater (Weber et al., 2020). This vitamin plays an intracellular role in bacterial oxidative metabolism and extracellular roles in bacterial quorum-sensing and plant-microbe interactions (summarized in Weber et al., 2020). Finding riboflavin in the exometabolome suggests that its extracellular roles are important in these communities, a conclusion that would have been missed or ambiguous had riboflavin been detected in bacterial isolates or tissue samples, the more common sampling approach.

Summary

1. New tools that enhance or bypass reference libraries and combine -omics approaches are enhancing our understanding of complex marine metabolomes and our ability to use metabolomics for hypothesis testing.
2. Metabolomics is a scalable tool that can identify the ultimate causes of physiological changes, be they in organelles or across ecosystems.
3. Studying the exometabolome, molecules released by organisms into their environment, simplifies molecular complexity to the most ecologically relevant components of the chemosphere.

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Conflict of interest

The authors declare that the work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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