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Review article

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The coral microbiome in sickness, in health and in a changing world

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Abstract

Stony corals, the engines and engineers of reef ecosystems, face unprecedented threats from anthropogenic environmental change. Corals are holobionts that comprise the cnidarian animal host and a diverse community of bacteria, archaea, viruses and eukaryotic microorganisms. Recent research shows that the bacterial microbiome has a pivotal role in coral biology. A healthy bacterial assemblage contributes to nutrient cycling and stress resilience, but pollution, overfishing and climate change can break down these symbiotic relationships, which results in disease, bleaching and, ultimately, coral death. Although progress has been made in characterizing the spatial-temporal diversity of bacteria, we are only beginning to appreciate their functional contribution. In this Review, we summarize the ecological and metabolic interactions between bacteria and other holobiont members, highlight the biotic and abiotic factors influencing the structure of bacterial communities and discuss the impact of climate change on these communities and their coral hosts. We emphasize how microbiome-based interventions can help to decipher key mechanisms underpinning coral health and promote reef resilience. Finally, we explore how recent technological developments may be harnessed to address some of the most pressing challenges in coral microbiology, providing a road map for future research in this field.

Sections

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Introduction

Coral reefs are the most biodiverse marine ecosystems on Earth that provide a habitat for about 30% of all marine species and essential ecosystem services[1]. These ecosystems are threatened by local (for example, overfishing, pollution and urbanization) and global (for example, ocean warming, ocean acidification, deoxygenation, etc.) anthropogenic impacts that often act together[2]. Since the 1950s, about half of the coral reef cover has been lost, and according to recent estimates 70–90% of global coral reefs may disappear even under the most optimistic 1.5 °C warming scenario[3].

Healthy reef ecosystems rely on stony corals, which are marine cnidarians that build the 3D framework of the reef by depositing calcium carbonate skeletons (Box 1). Corals engage in a multitude of symbioses with microorganisms, forming the so-called holobiont or metaorganism[4–6], acting as the 'engine of the reef'. The term holobiont is used to denote the entirety of microorganisms found associated with a host organism, whereas the term metaorganism is more restricted and typically refers to the host and microorganisms for which a function is either ascribed or assumed[7]. Most notably, corals associate with Symbiodiniaceae, photosynthetic endosymbiotic algae that live inside the coral tissue and are expelled upon stress (for example, heat waves), which leads to a loss of pigmentation of the coral tissue known as bleaching (as corals become white)[8,9]. However, there are many more microorganisms associated with corals, such as bacteria[10], archaea, fungi, viruses[11] and other microeukaryotes[12] that together comprise the microbiome. Emerging evidence suggests that the microbiome composition and activity are intimately linked to animal health and can be harnessed to improve stress resilience, which has accelerated research into the specific roles of diverse microorganisms and their putative use[13,14]. In particular, coral–bacterial association can be flexible and can, for instance, be altered to mitigate the effects of thermal stress through provisioning of beneficial bacteria that ultimately reduce coral mortality following thermally induced bleaching[15–18].

Currently, we are still far from a functional and mechanistic understanding of microorganism–microorganism and microorganism–host interactions[19]. To this end, most studies have explored the bacterial microbiome using 16S rRNA gene sequencing, which provides an overview of community composition, structure and dynamics. The general consensus is that the bacterial microbiome in corals is diverse, flexible and malleable. To increase our functional knowledge, recent efforts have focused on increasing the number of bacterial isolates (including genome sequencing) that enable mechanistic studies[20–22] together with interrogating metagenomics data and metagenome-assembled genomes (MAGs) to elucidate functional underpinnings of associated microbial communities[23–25]; using experimental platforms with standardized phenotype diagnostics to assess the impact of microbiome manipulation[26]; reconstructing the evolution of symbiotic relationships[27,28]; and measuring metabolic fluxes as well as metabolite assimilation (metabolomics) to infer holobiont nutrient cycling and functional interchange[9,23,29,30].

The importance of these bacterial assemblages to coral biology and its malleability holds promise for coral adaptation, conservation and restoration to support the future persistence of coral reefs[13,14,31–33]. In this Review, we present our current knowledge of the function and role of the bacterial microbiome in coral health and disease, and highlight the response of the host-associated bacteria to global change, which bears implications for coral reef conservation. Throughout, we discuss the specific knowledge gaps that need to be addressed to advance this field and provide an outlook and a future perspective of microbiome-targeted interventions that may facilitate coral and reef resilience.

Composition of the coral microbiome

Microbiome diversity, temporal and spatial variability, and heritability

Recent years have brought a changing imperative in life sciences, with an increased recognition that bacteria are functionally important for their hosts[4,5]. In this context, a multitude of studies have demonstrated (mostly through 16S rRNA gene sequencing) that some members of the coral microbiome are species-specific with evidence for phylosymbiosis (that is, the co-evolution of bacterial associates with their host)[27,34]. At the same time, bacterial microbiome composition is subject to change under different prevailing environments[15,28,35,36], with age[37], across seasons[38] and under stress[17] (Fig. 1). These bacterial arrangements are hypothesized to either represent an adjustment towards a more beneficial bacterial composition that promotes coral health, known as the coral probiotic hypothesis, or could also signal dysbiosis (that is, loss of homeostasis, which leads to an imbalance in the microbiome)[33]. However, the propensity for change (that is, microbiome flexibility)[16], is coral-specific. Indeed, species from the genus *Acropora* typically exhibit mostly plastic microbiomes[17,39], whereas others, such as *Pocillopora*, exhibit mostly consistent, stable microbiomes that change little[15,35,40], even under extreme stress[41], with exceptions[42]. Thus, the concept of a core microbiome may mean different things for different coral species, be restricted to defined environmental conditions and need to account for the notion that not all coral rely on their bacteria equally, and not all bacteria contribute equally to their host[16].

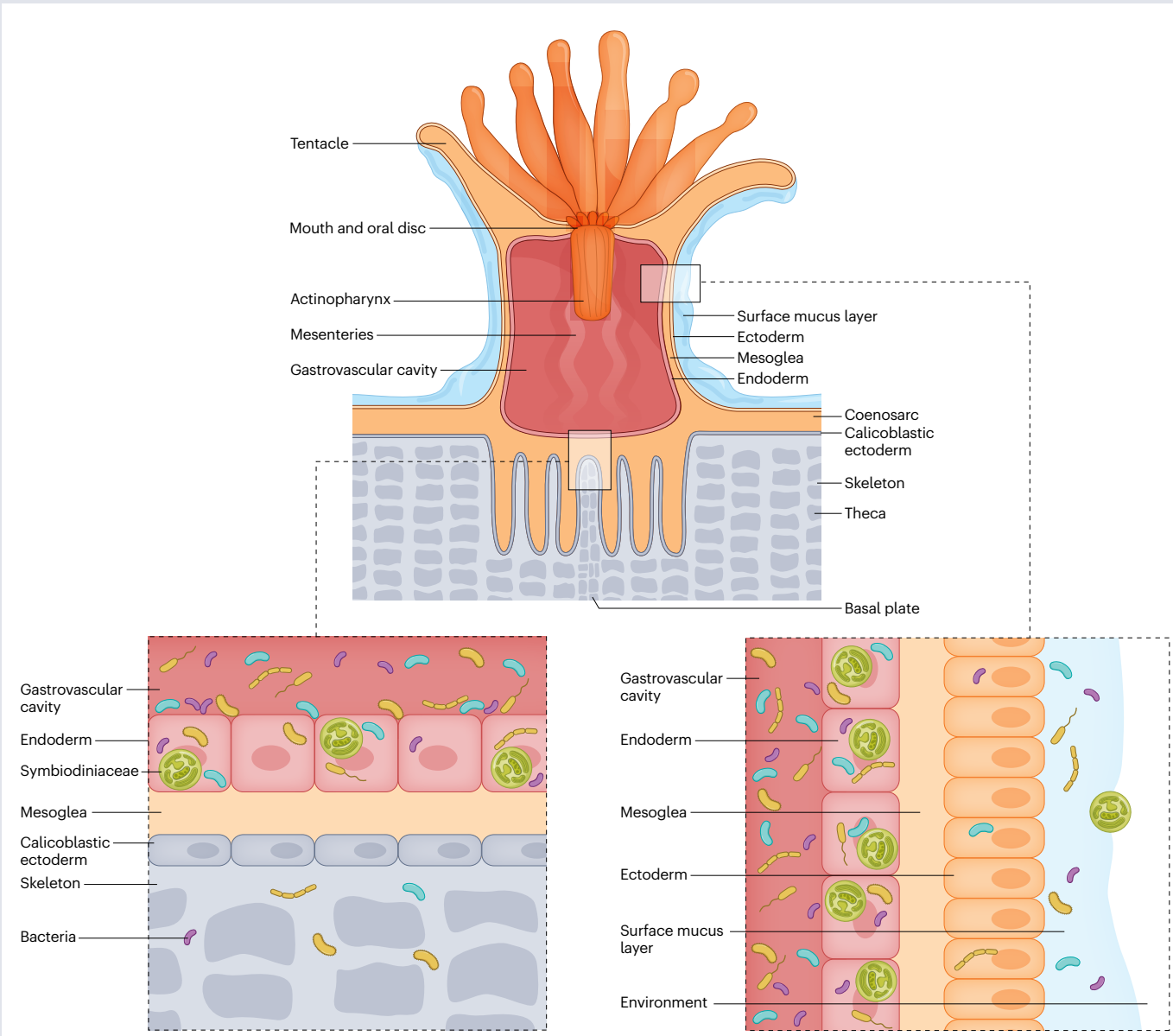
Some bacteria are transmitted from parent colonies to offspring[43,44] and persist despite a winnowing of the microbiome during coral larval development[37,45] and subsequent changes driven by prevailing environmental conditions[46,47] (Fig. 2). In addition, many bacterial taxa are suspected to be acquired from the environment at different life-history stages, or following changes in environmental conditions[10]. However, only a few studies thus far have addressed strain-level or population-level differences that may inform histories of co-diversification (or co-evolution), which are arguably important to identify stable bacterial symbionts from environmentally transient associations[28,48].

Although a high number of bacterial phyla (≥39) are reported to associate with corals[49], the most common are Pseudomonadota (previously Proteobacteria), Bacteroidota, Bacillota and Cyanobacteriota[49,50]. Among these, typical coral-associated bacterial families include Endozoicomonadaceae, Rhodobacteraceae, Vibrionaceae and Alteromonadaceae[10,51]. Some representatives from these families have been shown to be beneficial to corals, such as members of the genera *Alteromonas* and *Paracoccus*, whereas members of the genus *Vibrio* can be pathogenic[52]. Current estimates on the number of bacterial taxa associated with coral differ widely, and can range from tens to thousands of 'species' (amplicon sequence variants or operational taxonomic units)[27,34]. Such differences can be explained by discrepancies in analysis (for example, amplicon sequence variants can inflate 'species' estimates compared with operational taxonomic units because of intragenomic variations in 16S rRNA gene copies), sample collection (for example, whole coral versus tissue, mucus or skeleton) or sampling scale (single reef versus globally). A recent systematic study across the Pacific Ocean basin found that current estimates might be grossly underestimated owing to undersampling of reef biomes[53].

Box 1

Coral anatomy and compartments

Reef-building corals are marine benthic invertebrates of the phylum Cnidaria (which includes jellyfishes, sea pens and sea anemones) (Fig. 1). Although some species are solitary, most are colonial, composed of many identical and interconnected modules called polyps. Each polyp contains two cell layers — the ectoderm (or ectodermis) and the endoderm (also called endodermis or gastrodermis) — with an acellular layer (the mesoglea) in-between (see the figure). The ectoderm is in contact with the surrounding seawater and produces the surface mucus layer. This viscous secretion covers the surface of corals, protecting the colonies from environmental insults and assisting in prey capture. Polyps have a cylindrical shape and a sixfold symmetry, with an oral disk and a mouth at the top surrounded by a ring of tentacles. The mouth forms a boundary between the ectoderm and the endoderm, which lines the inner parts of the polyps and harbours Symbiodiniaceae. Directly below the mouth sits the actinopharynx, a tube that leads to the gastrovascular cavity, which fills the interior of the polyp and tentacles. The gastrovascular cavity contains the gonads and is partitioned by mesenteries, which are sheet-like folds of endoderm that increase the surface area for digestion and nutrient uptake.



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Adjacent polyps are connected by the coenosarc, which links gastrovascular cavities and enables the exchange of liquid, food or microbial symbionts. Finally, the basal cell layer (a modified ectoderm called calicoblastic ectoderm or calicoblastic ectodermis) deposits the calcium carbonate skeleton. The spatial structure of the polyp creates distinct physicochemical microhabitats or compartments (surface mucus layer, tissues, gastrovascular cavity and skeleton) that harbour different bacterial communities. At present, we still do not know in which compartment(s) most coral-associated bacteria reside; what the influence of anoxic microzones and other gradients on the metabolic activity of residing bacteria is; how connected these compartments are in terms of nutrient flows; or whether bacterial functions are spatially partitioned within a polyp. Fortunately, we are now equipped with a toolbox that can help to answer these pressing questions (Box 2).

The most prominent coral–bacteria association occurs with the gammaproteobacterial genus *Endozoicomonas* (family Endozoicomonadaceae). Members of this genus form cell-associated microbial aggregates in coral tissues and are thought to have a role in holobiont nutrient cycling and amino acid, organosulfur compound and B vitamin metabolism[22,25,54,55]. Notably, many coral species associate with multiple *Endozoicomonas* phylotypes, the functional significance of which is not well understood[28]. However, some evidence points to differing biogeographic patterns, which may indicate the presence of local variants that are fine-tuned to specific environmental conditions[28,35]. For instance, whereas the genus *Pocillopora* harbours a globally distributed *Endozoicomonas*, the coral genera *Porites* and *Stylophora* harbour site-specific phylotypes, which illustrates host differences in microbiome specificity and flexibility[25,35]. Nevertheless, a definitive role for *Endozoicomonas* is yet to be identified, despite numerous genomes, assemblage surveys and functional studies[22,35,54–57]. This can be due to the varying presence of *Endozoicomonas* with changing environmental conditions[15,36,58] and its broad, numerous and flexible association within host species and across different marine organisms[56], indicating that isolate-targeting laboratory studies are needed to establish the role of distinct *Endozoicomonas* bacteria[22]. Besides *Endozoicomonas*, many studies highlight the alphaproteobacterial genus *Ruegeria* in the family Rhodobacteraceae owing to its presumed interactions with other bacteria, Symbiodiniaceae and coral[59,60]. *Ruegeria* spp. are associated with many coral species[49] and constitute one of the few lineages that seem to consistently increase their relative abundance in corals under various stressors, including disease[61,62], which suggests that it is functionally important to coral health[18,63]. The recent improvement towards a fairly selective medium for coral-associated *Ruegeria* will facilitate isolation of strains[48], to investigate genetic variation at the population and strain levels, and their functional contribution to the coral holobiont.

Spatially complex coral compartments

A key factor that is likely to contribute to the variability of the bacterial microbiome is the spatial complexity of the coral holobiont (Box 1). Although corals are often considered structurally simple animals, they harbour nearly 40 different cell types[64] that are organized into two cell layers atop a porous aragonite matrix, the coral skeleton, creating distinct compartments[65]. This compartmentalization results in discrete microhabitats that differ in pH, light, dissolved oxygen and chemical profiles[66], fostering different bacterial communities[27,67]. Studies are increasingly performing spatially resolved sampling of the coral mucus, tissue (that is, ectoderm, mesoglea and endoderm), gastric cavity and skeleton[23,68,69]. However, bacterial communities can even be spatially structured at finer scales within these compartments[70], owing to the sharp physicochemical gradients present in corals[65,66].

Another contributor to spatial structure comes from the symbiotic association between bacteria and other coral-associated microorganisms[19], such as the attachment of specific intracellular bacteria (for example, *Hyphomicrobium*, *Methylobacterium* or *Sphingomonas*) with Symbiodiniaceae in hospite[68,71]. In addition, some bacteria (for example, *Endozoicomonas*, *Kistimonas*, *Aquarickettsia* or *Simkania*) form compact tissue-associated aggregates[35,72] that also contribute to the heterogeneity of the coral tissue. Given the tight spatial structures of the coral holobiont, identifying how specific bacteria associate with specific microhabitats is critical, as bacterial distribution within host compartments can provide important clues about their functions, and spatially resolved sampling will reduce discrepancies and variabilities observed when coral fragments are analysed whole (for example, controversy regarding core microbiome members). Indeed, the common 'bulk' approaches homogenize host cells, microorganisms and chemicals that may have been spatially separated, blurring the whole picture[73].

Knowledge gaps

Currently, we do not know how consistent coral microbiomes are over long periods of time, and how microbiome flexibility may be linked to the ability of the coral to withstand or adapt to different environmental conditions. This can be investigated using in situ automated sampling methods that capture the diversity and dynamics of coral microbiomes in their natural environment[74], which can help to pinpoint microbial associates that are strongly linked to specific environmental conditions. Such efforts might also support the delineation of defined 'ecotypes' (that is, ecologically relevant microbial taxa) to aid comparative analyses between studies[75]. Finally, the generalization of spatially resolved sampling will be critical to determine whether all coral compartments are equally affected by environmentally driven changes in microbiome composition. Further to this, colony surface heterogeneity (for example, disparate light microenvironments or differing distribution of microbial assemblage, trace elements and somatic mutations) and its consequences, such as differential bleaching susceptibility, need to be better understood[76–78]. We are also yet to comprehend the contribution of host genotype to bacterial association, and whether specific host genotypes form defined associations with distinct bacterial ecotypes, consequential to holobiont biology. Such interactions become even more complex when considering chimerism, which is common in some coral species, as a single colony may consist of multiple genotypes. Although not the focus of this Review, archaea and microeukaryotes are regarded as important holobiont members[12,79], in particular during bleaching and recovery[23,29,80]. With the exception of Symbiodiniaceae[8,28,81,82], we have no thorough functional, let alone mechanistic, understanding

of microbial–host interactions. Even in the case of Symbiodiniaceae, important discoveries on the mechanisms behind bleaching, nutrient cycling and host–symbiont recognition remained elusive until recently[9,83,84]. Thus, exciting discoveries with putative wide-reaching applications are on the horizon[14], facilitated by the development and extension of the available toolbox (Box 2).

Function of the coral microbiome

Metabolism, nutrient provision and energy transfer

Reef-building coral holobionts are characterized by their efficient cycling and recycling of nutrients[9,80], which enable them to inhabit highly oligotrophic environments[5]. Although historically the coral–Symbiodiniaceae relationship has been investigated through metabolic studies, biogeochemical and increasingly multi-omics studies suggest that bacterial and archaeal nutrient cycling contributes substantially to the metabolism of coral holobionts[22–24,29,85] (Table 1).

Arguably, carbon cycling is the foundation of metabolic interactions in the coral holobiont. Corals receive their energy in the form of organic carbon through translocation of photosynthates produced by Symbiodiniaceae[83], although the capacity for photoautotrophy is not limited to these algae. Members of the genus *Ostreobium* (Chlorophyta) photosynthesize in the low-light skeletal compartments of the holobiont[86] and their photosynthates may be exported to the coral tissue, which facilitates host survival in the absence of Symbiodiniaceae during bleaching[23,66,87]. Other primary producers, such as the alveolates *Chromera* and *Vitrella*, are also commonly found in the holobiont[88], but the nature of their interaction with the coral host is still not fully resolved[89]. In addition, coral-associated apicomplexans called

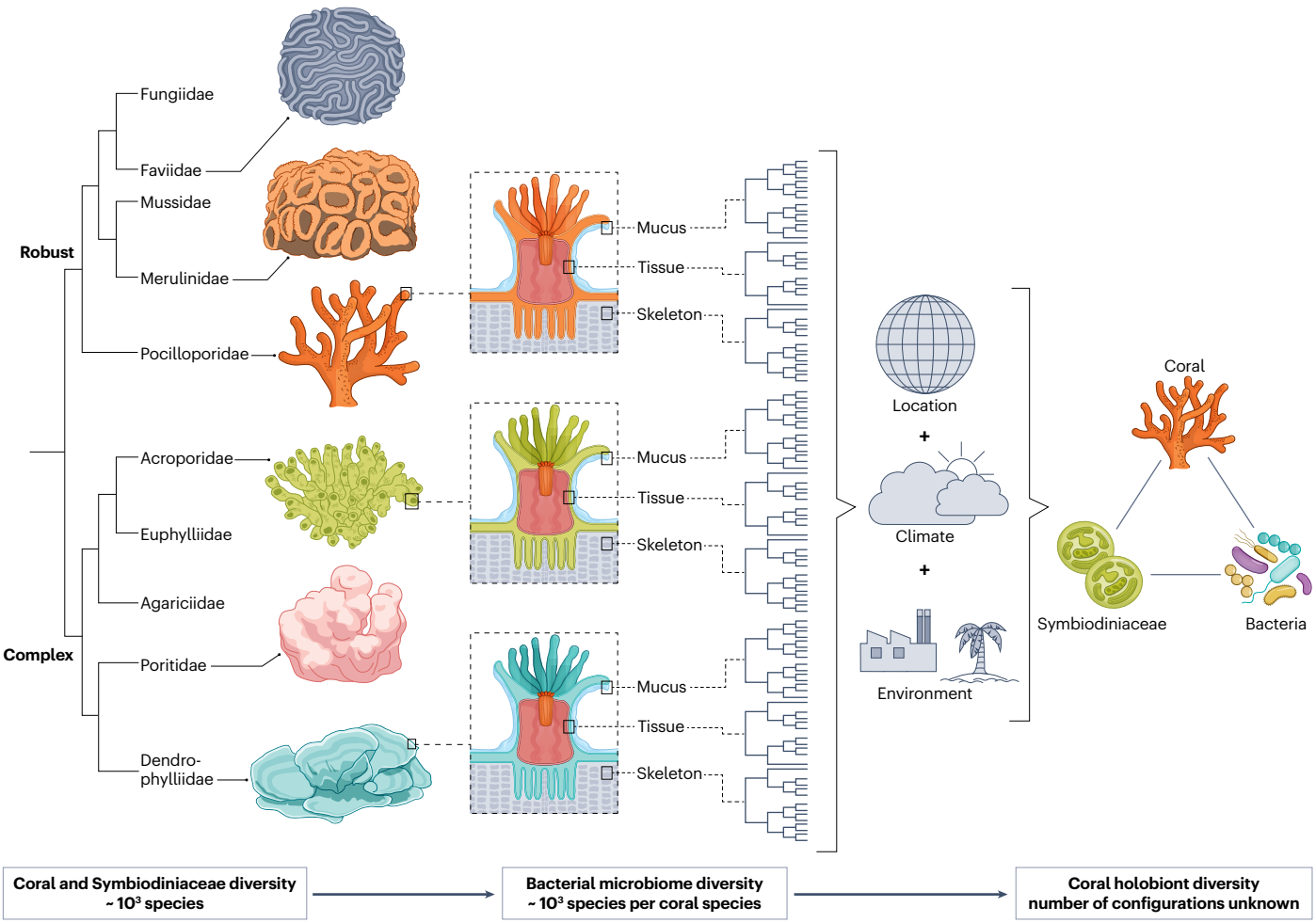

Fig. 1 | Coral and bacterial microbiome diversity. Stony corals are the foundation species of reef ecosystems that diverged into a robust and complex clade >250 million years ago. Through symbiosis with photosynthetic algae (Symbiodiniaceae), corals deposit calcium carbonate skeletons that build the 3D seascape of reef ecosystems that provide habitat for about a third of all marine species. Within the order Scleractinia, two major clades have been identified based on molecular data. Members of the 'complex' clade are not as heavily calcified as the 'robust' clade. Each of the >10^3 described coral species partner with specific Symbiodiniaceae (the total estimated diversity is 10^2–10^3 species) and are associated with ~10^3 bacterial species (tthe total estimated diversity is >10^6 species), many of which are compartment-specific (Box 1). Only very few of these bacteria have been isolated or are functionally understood. In comparison to the rather strict association with Symbiodiniaceae, bacterial assemblages tend to be more dynamic and associations change because of differences in location, climate and environmental conditions. This flexible association with bacteria contributes to the complexity of the microbiome and further complicates its study, as each combination of location, climate and environment leads to a distinct coral holobiont configuration. At the same time, the built-in flexibility provides the foundation for active intervention by means of microbiome manipulation (for example, by means of microbiota transfer therapy through probiotic exposure).

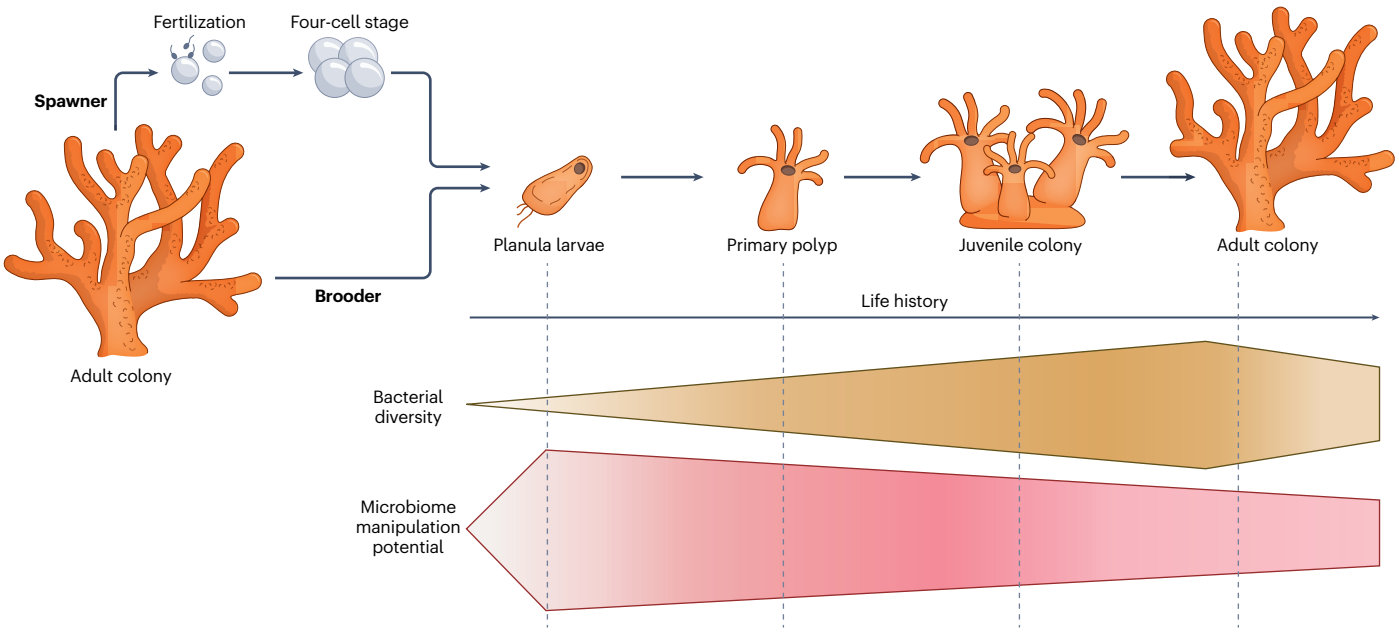

Fig. 2 | Bacterial colonization and succession of corals over their life stages. Corals reproduce by means of spawning or brooding. Spawning corals release bundles of egg and sperm into the water column (external fertilization), whereas brooding corals release planula larvae (internal fertilization). Gamete bundles and released planula larvae were both shown to contain bacteria from their parental colony, thereby ascertaining a mechanism to vertically transmit bacteria (from parent to offspring). During all life stages, corals are assumed to acquire bacteria from the environment. Bacterial diversity is typically low in early life stages and increases during larval stages. During the course of development, corals undergo changes in their bacterial diversity, which eventually results in a stable, consistent bacterial microbiome[44,196,197] (indicated by the colour gradient and shape of the polygon)[196,197]. Notably, microbial diversity is a dynamic entity that can increase or decrease depending on the prevailing environment and health state of a coral[15,17,36,198]. Given the highly dynamic restructuring of bacterial and algal communities in juvenile coral, microbiome manipulation is likely to be more feasible in early life stages (indicated by the colour gradient and shape of the polygon)[199,200]. As for the bacterial diversity, malleability is influenced by many environmental factors as well as the health state of the coral itself. Currently, the temporal stability of microbiome manipulation measures is unknown, as is whether persistence of inoculated bacteria is required to retain altered physiological states.

corallicolids are abundant in coral tissue[79]. Although corallicolids are unlikely to be photosynthetic, they still harbour chlorophyll biosynthesis genes, indicative of a transition from phototrophy to parasitism[79]. Besides these eukaryotes, bacterial and archaeal autotrophs are highly diverse and many of them can use anoxygenic photosynthesis, a process that converts light energy into ATP without generating oxygen[23,24,90–92]. Furthermore, viruses may affect holobiont productivity by affecting Symbiodiniaceae and bacterial abundances[93,94] and contributing to the diversity of metabolic genes within the bacterial community[95,96] (Box 3).

Uptake of exogenous dissolved organic carbon (DOC) through heterotrophy constitutes another source of carbon for the holobiont[97,98]. However, the consumption and transformation of DOC by heterotrophic microorganisms in the water column can affect holobiont health: elevated DOC concentrations can increase bleaching susceptibility[99] and are linked to an increase in microbial biomass (microbialization)[100], which contributes to the ongoing degradation of coral reefs. Related to this, the DDAM (dissolved organic matter, disease, algae and microorganism) model proposes that resident opportunistic microorganisms may contribute to pathogenesis when stimulated by algae-released DOC[101,102].

Besides carbon, nitrogen cycling also has a key role in coral holobiont integrity and functioning[80] (Table 1). Healthy reef-building coral holobionts are nitrogen-limited, which is critical to Symbiodiniaceae symbiotic maintenance[9,84,103]. One source of nitrogen is dinitrogen (N_2) fixation, which yields 'new' bioavailable nitrogen to support holobiont primary productivity[104]. Diazotrophs, bacteria and archaea that fix nitrogen into bioavailable ammonia ubiquitously associate with reef-building corals[24,105,106]. The fixed nitrogen is assimilated by the coral host and Symbiodiniaceae[29,104,107]. Although diazotrophy increases under heat stress[108], the nitrogen surplus is not assimilated by the coral or Symbiodiniaceae[29]. Thus, reliance on diazotroph-derived nitrogen depends on the holobiont nutritional status and the environmental context[29]. Unlike N_2 fixation, other nitrogen cycling pathways such as nitrification, denitrification and anaerobic ammonium oxidation (ANAMMOX) have received limited attention[109,110]. Denitrifiers are ubiquitously associated with corals and seem to be specific to the host species, Symbiodiniaceae lineage and nutrient environment[110–112]. Positive correlation of denitrification rates and Symbiodiniaceae density in stony corals suggests denitrifiers may be located close to Symbiodiniaceae, allowing them to interact and benefit from photosynthate availability[110].

Sulfur cycling has been extensively investigated in corals, as the holobiont produces the largest amount of dimethylsulfoniopropionate (DMSP) measured in the environment[113]. This organic sulfur molecule can function as a chemoattractant, an antioxidant, a cryoprotectant, an osmolyte, an important source of carbon or reduced sulfur for marine bacteria and the main precursor of dimethyl sulfide (DMS), which is a climate-active gas involved in cloud formation[114] (Table 1). Corals harbour diverse microbial communities involved in cycling DMSP and other related methylated sulfur compounds. Indeed, some abundant coral-associated bacteria can produce DMSP from

Box 2

A toolbox to address pressing challenges in coral microbiome research

To identify which bacterial functions are critical for coral holobiont functioning, hypotheses derived from meta-omics approaches (for example, metagenomics, metatranscriptomics, metaproteomics or metabolomics) could be validated by inoculating gene knockout mutants (for example, genetically modified bacteria devoid of a specific functional gene) to model host species (for example, Aiptasia or *Galaxea fascicularis*). The use of gnotobiotic (that is, bacteria-depleted)[149] and ultimately axenic (that is, bacteria-devoid) hosts will enable the identification of key host–bacteria and bacteria–bacteria interactions with even greater accuracy. In addition, the quantification of specific functional traits between coral species or environments could be achieved through quantitative PCR assays[201] targeting an extensive range of marker genes[110]. As selection acts on phenotypes, regardless of their genomic underpinning, different bacteria could have the same function in different corals. It also means that inferring the absence of a function based on the absence of specific bacteria from a sample is likely to be erroneous.

To characterize bacterial activity and ecology at scales that are relevant to associated microorganisms, spatially targeted sampling (such as laser-capture microdissection or other micro-sectioning approaches) can be coupled with whole-genome amplification[68,72,122] and low-input omics approaches[202,203]. These techniques can determine the taxonomic, functional or chemical characteristics of specific microenvironments, separating, for example, the gastric cavity fluid, the surface mucus layer and specific tissue-associated aggregates. In addition, mass spectrometry imaging enables quantifying nutrient fluxes between partners (for example, using nanoscale secondary ion mass spectrometry (NanoSIMS))[9,23], or the spatial location of individual molecules (for example, using matrix-assisted laser desorption/ionization)[30], with nanometre to micrometre resolution. These powerful imaging approaches can be coupled with fluorescent in situ hybridization[68,122], which stains specific bacterial taxa, enabling to clearly identify the location, metabolic activity and chemical landscape surrounding specific bacteria in the holobiont.

To scale up microbiome-based interventions (for example, probiotic therapy), multiple approaches are currently being explored as delivery strategies. These include bioencapsulation[204], inorganic carriers, inoculation of bacterial cells on biodegradable carrier material that releases cells slowly and constantly over time, or the use of biopolymers for spatial entrapment[31]. Strategies to prolong the shelf-life of microorganisms, such as lyophilized or freeze-dried probiotics[205,206], as well as the development of automated delivery systems are also being explored. This research frontier is at the interface of biology and engineering and is aimed at delivering innovative solutions to increase coral resilience.

methionine (for example, members of the *Shimia* genus)[115], degrade DMSP into DMS (for example, *Roseobacter* or *Endozoicomonas*)[55,59], demethylate DMSP to form methanethiol (for example, *Ruegeria*)[116] or further degrade DMS (for example, *Alteromonas* or *Hyphomicrobium*)[59], thereby reducing its emission from corals. Because of its functional significance, the capacity to degrade DMSP is considered a beneficial bacterial trait[31,117]. Some coral-associated bacteria can also use inorganic sulfur as electron acceptors instead of oxygen. For example, sulfate-reducing bacteria (SRB) are abundant in the coral skeleton[23,118] and may also inhabit other anaerobic microhabitats. SRB perform anaerobic respiration, degrading organic compounds while reducing sulfate or, in many cases, other oxidized inorganic sulfur molecules[118].

Corals and their Symbiodiniaceae are auxotrophs for B vitamins and must obtain them through their diet or from microbial symbionts[119]. Many coral-associated bacteria carry the biosynthetic gene clusters necessary for production of B vitamins, including thiamin (vitamin B_1), riboflavin (vitamin B_2), pantothenate (vitamin B_5), pyridoxine (vitamin B_6), biotin (vitamin B_7), folate (vitamin B_9), cobalamin (vitamin B_{12}) or tetrahydrofolate (coenzyme F)[21,22,24,25,54] (Table 1). The production of several B vitamins was confirmed in cultures of coral bacterial isolates[119,120] and coral-derived chemical cues increased protein abundances associated with biosynthetic gene clusters for thiamine, pyridoxine and biotin in *Endozoicomonas marisrubri* 6c[22]. Essential vitamin production by host-associated bacteria could partially explain their importance to the coral and also how a dysbiotic microbiome (see below) could further exacerbate coral stress, disease or bleaching.

Inter-species interactions

Bacteria possess many different 'nanomachines' that can secrete a wide range of compounds in their surroundings or inoculate them directly into adjacent eukaryotic, bacterial or archaeal cells[121]. These secretion systems are therefore important for inter-species interactions and are commonly found in coral-associated bacteria, specifically type II, type III, type IV and type VI secretion systems[22,57,72,122]. Secretion systems are not restricted to pathogenic interactions. They are also commonly found in commensal bacteria, conferring fitness advantages in host manipulation and colonization, and are potentially involved in horizontal gene transfer (HGT), interbacterial competition and antagonism[102,123,124]. Type II secretion systems are prevalent in coral-associated Gammaproteobacteria, particularly in the Endozoicomonadaceae and Vibrionaceae families[21,22]. Type VI secretion system-related domains are abundant in putative pathogens such as *Vibrio* spp.[21] and present in reconstructed MAGs of uncultured *Endozoicomonas*, although they have not been reported from cultured *Endozoicomonas* strains to date[72].

Eukaryotic-like protein (ELP) effectors mediate protein–protein interactions pertaining to an intracellular lifestyle and have been suggested as modulators of eukaryote–bacteria interactions during symbiosis establishment[125]. This group includes ankyrin, tetratricopeptide, WD40 and leucine-rich repeats as well as zinc finger and ephrin-binding domains present across the genomes of coral-associated bacteria[21,22,24,25,57]. ELP effectors are common and abundant in the genomes of tissue-associated bacteria (for example,

Endozoicomonadaceae) and in the bacterial metagenomes recovered from visibly healthy corals[21,22,24,126]. Upregulated gene expression of several ELPs in the coral symbiont *E. marisrubri* 6c in response to chemical cues of its coral host suggests a role of ELPs in infection and symbiosis establishment[22].

Role in coral health, disease and stress resilience

Despite the description of more than 40 coral diseases since their first report by Antonius in 1973, only a few coral pathogens have been identified[127]. Among these disease-causing agents, two *Vibrio* spp., *Vibrio coralliilyticus* and *Vibrio shilonii*, have been extensively studied

Table 1 | Summary of confirmed and proposed functions of coral-associated bacteria

Function	Organisms involved	Location	Confirmation and methods	Refs.
Metabolism				
Nitrogen fixation	Heterotrophic diazotrophs (mostly Alphaproteobacteria and Gammaproteobacteria) and cyanobacteria transfer nitrogen to the coral host and Symbiodiniaceae	Tissue, skeleton	**Confirmed** Nitrogenase activity (acetylene reduction assay), enzyme detection (immunogold labelling), marker gene amplification (*nifH*), fluxes of fixed nitrogen (NanoSIMS)	29,104–106
Nitrification	Autotrophic bacteria and archaea transfer nitrogen to other, uncharacterized holobiont members	Mucus, tissue, skeleton	**Confirmed** Nitrification rates, marker gene amplification (*amoA*)	109
Denitrification	Heterotrophic bacteria transfer nitrogen to other, uncharacterized holobiont members	Tissue, skeleton	**Confirmed** Denitrification rates, marker gene amplification (*nirS*, *nirK*)	110,112,188
Carbon fixation	Autotrophic bacteria and archaea transfer organic molecules to other, uncharacterized holobiont members	Tissue, skeleton	**Hypothesized** Presence of multiple pathways in MAGs	23,24
B vitamins	Heterotrophic bacteria transfer vitamins to other, uncharacterized holobiont members	Gastric cavity	**Indirect** Vitamin B_{12} concentrations (radio-assay), presence of multiple pathways in MAGs, production in cultures	21,22,24,25, 54,119,120
Growth-promoting hormones	Heterotrophic bacteria transfer growth-promoting hormones to Symbiodiniaceae	Tissue	**Indirect** Transfer of indole-3-acetic acid in co-cultures with Symbiodiniaceae	189
Organic sulfur cycling	Heterotrophic bacteria synthesize or catabolize organic sulfur compounds that are then transferred to other, uncharacterized holobiont members	Mucus, tissue, skeleton	**Confirmed** Production and degradation activity (in vitro assays), marker gene amplification (*dmdA*, *ddd*), uptake of organic sulfur (NanoSIMS)	55,59,115, 116,190
Sulfate reduction	SRB transfer sulfide to green sulfur bacteria	Skeleton	**Hypothesized** Marker gene amplification (*dsrA*), presence of pathways in MAGs	23,118
Signalling and immunity				
Settlement cues	Bacterial biofilms on surfaces induce the settlement of coral larvae	External substrates	**Confirmed** Larval settlement assays, isolation of metamorphosis cue from Gammaproteobacteria	191
Immune system evasion	Tissue-associated bacteria use ELPs to establish their intracellular lifestyle	Tissue	**Hypothesized** Presence of ELP effectors in the genome of many coral-associated bacteria	21,22, 24,126
Stress resilience				
Antioxidant	Heterotrophic bacteria produce antioxidants (for example, superoxide, DMSP, zeaxanthin) decreasing oxidative stress in the coral host and Symbiodiniaceae	Tissue	**Indirect** Production of antioxidant molecules in co-cultures with Symbiodiniaceae	192,193
Antimicrobial	Heterotrophic bacteria produce compounds inhibiting the growth of pathogens	Mucus, tissue	**Confirmed** Antimicrobial activity assays, isolation of antimicrobial compounds	60,136,138, 140,194
Osmolyte	Heterotrophic bacteria produce higher concentrations of osmolytes under salinity, thermal or UV stress	Mucus, tissue	**Indirect** Presence of pathways in MAGs and isolates; production in isolates under stress (in vitro assays)	85,115,195
Microbiome restructuring	Bacterial assemblage adjusts to the prevailing heat stress environment, enriching for functions related to carbohydrate, nitrogen or ROS metabolism	Unknown	**Hypothesized** Enrichment of functions associated with increased abundance of mostly Alphaproteobacteria under heat stress	17

DMSP, dimethylsulfoniopropionate; ELP, eukaryotic-like protein; MAG, metagenome-assembled genome; NanoSIMS, nanoscale secondary ion mass spectrometry; ROS, reactive oxygen species; SRB, sulfate-reducing bacteria.

and are directly associated with the development of some incidences of coral bleaching and white syndrome, respectively[128,129]. Although the infection mechanisms of these two pathogens have been well characterized, the causative agents of other widespread diseases remain unknown. For example, stony coral tissue loss disease (SCTLD) affects more than 20 coral species in the Caribbean and is characterized by rapidly spreading lesions and high mortality rates, making it one of the deadliest coral diseases on record[130]. Several lines of evidence suggest that viral infection is implicated in SCTLD pathology[131,132], yet it is unclear whether viruses have a primary or a secondary role in this infection. Some other coral diseases do not seem to fit the one pathogen–one disease paradigm generally postulated for many biological systems[133,134]. A key example is black band disease, which is caused by a complex microbial consortium including cyanobacteria, SRB as well as a diverse range of heterotrophic bacteria, archaea, fungi and other microeukaryotes[135]. The cyanobacteria-dominated consortium performs photosynthesis during daylight and respiration at night, which fuels contrasting diel metabolic activities of a diverse assemblage of heterotrophic bacteria, SRB (*Desulfovibrio*) and sulfur-oxidizing bacteria (*Beggiatoa*), resulting in steep gradients of oxygen and sulfide that are lethal to the underlying coral tissues[135].

A wide span of bacterial taxa can produce compounds that affect the growth of microbial competitors. Common antimicrobial-producing bacteria include members of *Pseudoalteromonas*, *Streptomyces*, *Bacillus*, *Pseudovibrio* and *Pseudomonas*[136–138], and members of these genera can inhibit the growth of the pathogens *V. shilonii*[60], *V. coralliilyticus*[60,138], *Vibrio owensii*[138], *Thalassomonas loyana*[60] and *Serratia marcescens*[139]. In addition, the inoculation of coral fragments with a specific *Pseudoalteromonas* strain with broad-spectrum antibacterial activity slowed, or in some cases even arrested, progression of SCTLD[140]. Although only two antimicrobial molecules have been isolated to date from coral-associated bacteria, tropodithietic acid[138] and korormicin[140], genomic evidence suggests that the number of antimicrobial compounds produced in the holobiont is much

Box 3

Coral-associated bacterial viruses

Corals harbour a diverse and abundant virome, with more than 60 viral families identified in corals worldwide[95,207]. A few viral families that belong to three major viral lineages are ubiquitously observed in corals and are predicted to infect coral cells as well as Symbiodiniaceae, bacteria and archaea[11]. Although Symbiodiniaceae-infecting viruses conceivably contribute to coral bleaching and mortality[93,208], here we focus on viruses that infect bacteria, among which double-stranded DNA viruses of the Caudoviricetes class (tailed phages) are dominant[95]. Studies investigating the coral virome to date have used a taxonomic framework that classified these viruses into families based on the viral particle morphologies of representative members (Podoviridae, Myoviridae and Siphoviridae). This framework does not reflect viral evolutionary lineages or genomic composition and has been phased out by the International Committee on Virus Taxonomy (ICTV)[209]. Therefore, a major re-evaluation of the diversity and composition of the coral virome under the light of genome-informed taxonomy is due.

Although the exceeding genetic diversity and abundance of viruses in coral tissues and mucus are clear, their roles in coral holobiont functioning are still poorly understood. Recent evidence from ultrastructural and molecular studies indicates that filamentous viruses infecting Symbiodiniaceae are involved in the response of corals to stress and, possibly, in disease aetiology[93,131]. Among bacterial viruses, filamentous single-stranded DNA viruses have been implicated in the emergence of potential opportunistic pathogens through the lateral transfer of virulence genes to bacteria[210,211]. Filamentous single-stranded DNA viruses were considered dominant members of the coral microbiome in the past owing to amplification biases in the sequencing of coral viromes but are now assumed to be present in low abundance in coral tissues[95,207]. Likewise, abundant tailed phages infecting bacteria have been isolated from cyanobacteria causing black band disease and have been experimentally demonstrated to mediate the competition between commensal and pathogenic bacteria, which leads to tissue loss and eventually death of the coral host[212,213]. Mounting genomic evidence also indicates that tailed bacterial viruses participate in ecological interactions of corals at the reef scale, such as the competition with other holobionts for benthic space[214] and the switch between a free-living and a coral-associated lifestyle in bacteria[215,216]. Whether these community dynamics are a cause or a result of biological processes occurring in the coral and bacterial host remains to be tested experimentally for the majority of cases[213,217].

Free-living bacteriophages that inhabit the reef boundary layer are also tightly linked with coral holobiont health. The diversity and functional profiles of these viruses are strongly predicted by the composition of the benthic community[218]. Corals and algae select distinct bacterial members in the water overlaying them by releasing organic matter with distinct chemical composition, and the viral community, in turn, responds to the availability of bacterial hosts[219]. These trophic relationships establish strong feedback loops between the benthic and free-living communities. As a result, the predation pressure that viruses exert on bacteria that inhabit the reef boundary layer is a strong predictor of the amount of live coral cover on Pacific coral reefs[220].

Events of high viral lysis have been observed in the water column and boundary layers of several reefs[221], causing high rates of bacterial mortality. A decrease in reef viral predation pressure can be caused by a switch from a predator–prey lytic dynamic to temperate viral infections[222]. This not only lifts the lytic control on bacterial growth, which may lead to hypoxia and coral tissue necrosis, but also facilitates horizontal gene transfer (HGT) that may be detrimental to corals. Many temperate viruses in coral reefs encode virulence genes that turn bacteria pathogenic to animals[95,216,223]. Given the importance of viruses to coral and reef health, phage therapy is a promising tool for restoration or rehabilitation processes. However, owing to potential off-target effects and uncontrolled expansion, this approach is not currently considered in the wild[14].

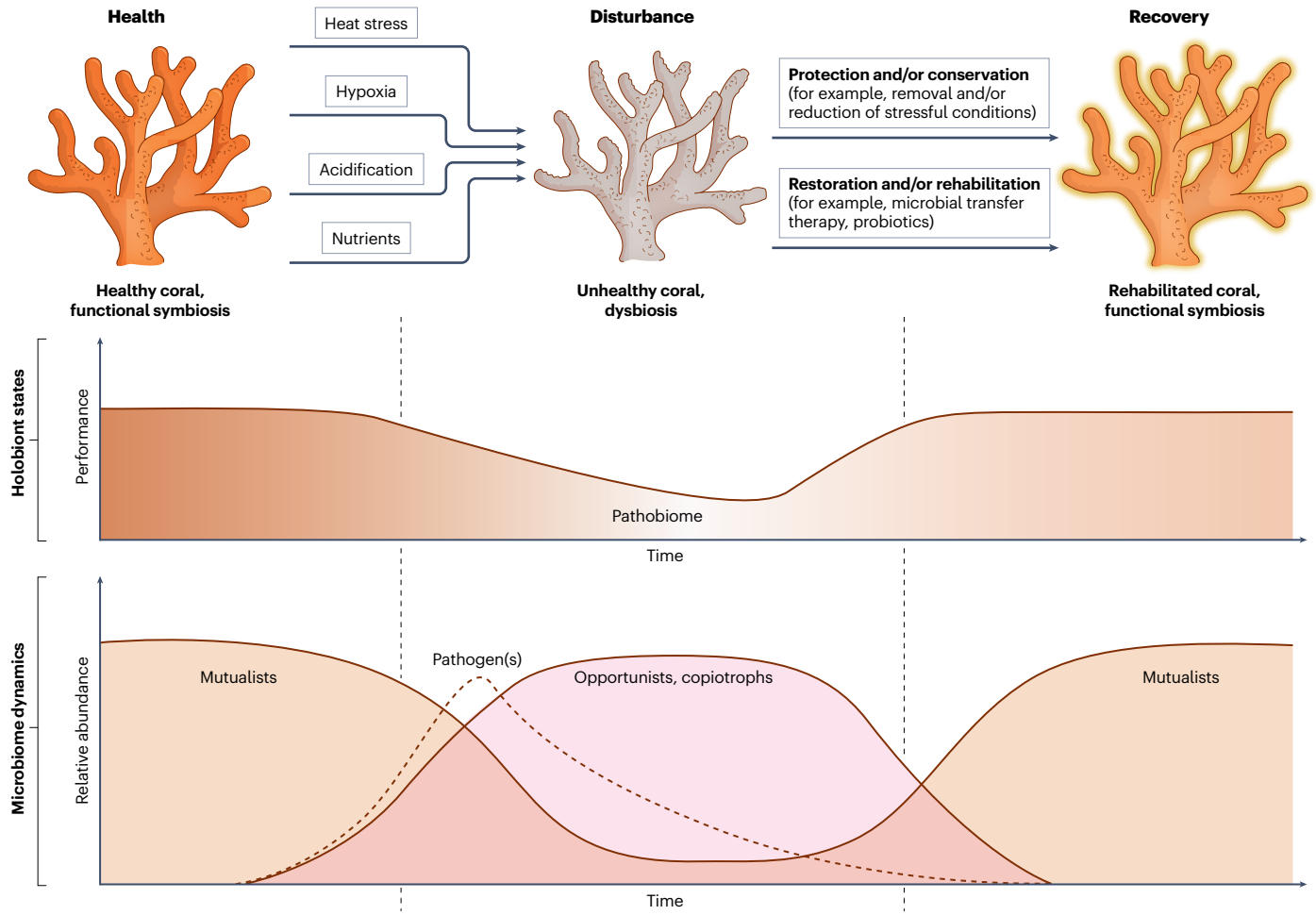

Fig. 3 | Coral health in a changing world and the role of the microbiome for reef conservation and management. Healthy corals engage in functional symbioses with a suite of beneficial, mutualistic microorganisms. Upon stress (such as nutrient, heat or hypoxia), the homeostatic assemblage is disturbed, and either the entrance of pathogens or the propagation of opportunists (copiotrophs) is facilitated, whereas the abundance of (host-)specific microorganisms decreases[134,135,142]. Once the coral holobiont is in a compromised state, opportunistic, copiotrophic bacteria can occupy the available niches and exploit their resources, giving rise to the pathobiome[133,142]. Removal or reduction of the stressful conditions helps to maintain or restore symbiotic relationships, while discouraging pathobiotic associations. Microbiome-based active interventions such as microbial transfer therapy or probiotic provisioning can rehabilitate coral holobiont health by restoring functional symbioses through either resetting or reprogramming the microbiome. The latter can lead to an altered microbiome.

larger[140]. The growth inhibition of coral pathogens by a large range of coral-associated bacteria suggests that the production of antimicrobial compounds has a role in the prevention of coral disease. Concomitantly, compromised coral microbiomes are less capable of thwarting pathogens, thus connecting coral disease to microbiome dysbiosis and coral health.

Understanding the evolution of a pathogenic microbiome (that is, the pathobiome) from a healthy microbiome is crucial to characterize coral disease aetiology[133,134]. Although defining the healthy microbiome can be difficult owing to the complexity of the microbial communities and their spatial and temporal variations (discussed above), it is essential to strike a balance between studying healthy and diseased states, recognizing that the two are interconnected and that insights into the mechanisms underlying both are essential for improving our understanding of coral performance (Fig. 3). For instance, one of the hallmarks of dysbiosis is an increase in the β-diversity of microbiomes, which is characterized by an increase in the dissimilarity between microbial communities often accompanied by an increase in copiotrophs and opportunistic pathogens. This increase in β-diversity may involve a loss of host control over community composition and stochastic community responses to external perturbations[141–143] (Fig. 3). A microbiome shift towards more abundant pathogens and/or depletion of symbionts not only affects coral performance but supports the development of disease[144]. However, coral microbiomes can also exhibit major shifts in response to various factors, which may be leveraged to enhance coral resilience and aid environmental adaptation[14,16]. For instance, recent microbiome manipulation studies have focused on the application of probiotics or field-based coral microbiome transplantation as a means of providing beneficial bacteria to increase coral heat tolerance or recovery from bleaching[18,145].

Knowledge gaps

Despite recent advances, the mechanisms by which bacteria from the coral microbiome exert specific functions are largely unknown (Table 1). An ongoing debate in microbiome research addresses to what extent taxonomy is indicative of function and whether useful measures can be derived from comparing taxonomy with function (for example, diversity, stability or health)[46,146]. Although the promise of microbiome manipulation to increase coral performance has been shown in principle, it is unclear whether it is applicable broadly across species. Will we be able to design a universal probiotic cocktail that can make corals resilient across species and environments, or do these probiotics need to be custom-made for each host and environment? Another challenge is understanding the scalability of microbiome interventions and whether successful attempts in laboratory studies and small-scale field studies can be scaled to larger populations and ecosystems. Application of probiotics has broad uptake in aquaculture-related industries and the development of similar approaches to an expanding coral aquaculture sector to supply burgeoning reef restoration endeavours is perhaps the first attainable step[147]. Nevertheless, it is important to determine how long the effects of microbiome interventions last and whether they can persist over time, as this will determine the scale of effort required (that is, single administration versus repeated provisioning). Answering these questions will have important implications for coral conservation efforts, with the research conducted during this process facilitating a greater understanding of the underlying host–bacterial mechanisms that underpin coral health. For instance, if probiotic exposure triggers epigenetic changes in the host, then this will likely constitute a long-term intervention[148]. The use of model organisms, such as Aiptasia or *Galaxea fascicularis*, to experimentally manipulate holobiont configurations (for example, by adding bacterial isolates or rendering the host gnotobiotic) under laboratory conditions will also help to identify the molecular underpinnings of coral holobiont homeostasis and resilience[26,149,150]. Finally, the extent and pace of natural adaptation and the role of the microbiome in this process need to be better understood. One of the adaptive mechanisms is HGT, a substantial driver of microbial evolution that can lead to the acquisition of new traits and functions, including antibiotic resistance, virulence and metabolic capabilities[151]. Clearly, more work is needed to understand the role HGT has in coral health and disease and which microbiome members are critical for HGT to influence host adaptation.

The coral microbiome and global change

Effects of climate change on the coral holobiont and microbiome

Climate change negatively affects the health of corals by simultaneously affecting water temperatures, salinity, oxygen levels and pH. Ocean acidification induces a reduction in carbonate ions, decreasing the rate at which corals deposit their calcareous skeleton[152]. Thermal stress notoriously triggers the loss of Symbiodiniaceae from coral tissue, causing coral bleaching[153]. Depending on the intensity and duration of the heat anomaly, bleaching can be fatal. Even when corals recover, bleaching durably affects their growth, reproduction, tissue thickness and immune system[154,155], opening the door to pathogen infections[156]. Abrupt variations in salinity, owing to the amplification of the global hydrological cycle, result in osmotic stress and can lead to the loss of Symbiodiniaceae[157]. Finally, ocean deoxygenation, caused by the warming of surface waters and the increase in nutrient runoff, can induce hypoxia in corals, when the oxygen supply is insufficient to sustain normal functioning and can cause mortality because of low ATP production[158].

Similar to the coral host, bacteria are sensitive to environmental perturbations imposed by climate change[13,159]. Even though the effects of thermal stress and ocean acidification have received far more attention than salinity stress and deoxygenation, commonalities emerge in the short-term responses of the coral microbiome to all these stressors. Some coral genera, such as *Pocillopora*, have a rather stable microbiome that often remains unaltered during exposure to environmental stress[15,41,42]. However, many other coral genera, such as *Acropora* and *Porites*, typically exhibit rapid shifts in their bacterial communities, with a decrease in the relative abundance of Endozoicomonadaceae and an increase in Vibrionaceae, Alteromonadaceae or Rhodobacteraceae[15,160]. Further to this, the virulence of several coral pathogens is increased at elevated temperatures[161–163]. In most cases, the microbiome typically reverts to its initial state once stressful conditions subside[15,51]. Although these short-term microbial dynamics are relatively easy to characterize through controlled laboratory experiments, long-term changes are harder to track and predict. Extreme environments, such as highly acidic CO_2 seeps or thermally variable back-reef pools, provide very useful windows to better understand these long-term changes[17,106,164] and to correctly predict the role of bacteria in aiding host adaptation in the future.

Besides changing abiotic factors, it is important to note that biotic factors can influence the coral bacterial microbiome. For instance, predators' mouths, faeces or physical contact with other organisms, such as competitors (for example, algae), can transfer bacteria to corals and affect their microbiome[93,143,161,165,166]. In particular, corallivores (such as reef fishes, echinoderms, molluscs or crustaceans) can be vectors and reservoirs of coral pathogens that can colonize abrazed or damaged coral tissues[161,167]. Increased prevalence of coral disease could therefore be (at least partially) promoted by a positive feedback loop between rising seawater temperatures (and/or the increased presence of other stressors), which facilitates corallivore-driven pathogen invasion and overgrowth by space-competing algae. These processes increase coral mortality and further support higher algal abundance[161].

A general signature of the microbiome in the Anthropocene — for organisms and ecosystems alike — is an increase in diversity and a decrease in evenness, typically linked to a decrease of host-specific microorganisms and an increase of opportunistic bacteria and pathogens[168] (Fig. 3). However, such changes seem rather haphazard[141], making it challenging to define specific bacterial taxa as biomarkers to denote degraded host or ecosystem states. Things are further complicated by the plasticity or flexibility of the microbiome (for example, inconsistency of microbiome assemblage across sites and ability to respond rapidly to environmental changes), or the general lack of understanding of what constitutes a healthy microbiome[159].

Implications for coral reef conservation and management

If we accept that healthy microbiomes are linked to healthy hosts that are in turn linked to healthy ecosystems, then the concept of microbiome stewardship becomes central to managing coral reefs[13]. The management of ecosystem resources should therefore include an understanding of how the microbiome facilitates organismal and ecosystem functions[13]. Despite our limited knowledge on specific microorganisms, microbial interventions can empirically be tested to improve coral health, increase stress tolerance or improve recovery. For instance, despite the vague definition of a healthy coral microbiome being an assemblage of bacteria that are either neutral or beneficial to the holobiont, microbial groups and functions important to a healthy microbiome can be identified through isolation of bacterial strains, testing for

the presence of beneficial traits in vitro and conferral of these traits in situ[18,61]. Microbiome-targeted interventions seem to be very valuable to support organismal and ecosystem resilience by restoring symbiotic interactions and preventing dysbiotic processes (Fig. 3). This is achieved, for instance, by rebooting the microbiome through provisioning of microbiome consortia (or specific isolates) from healthy donor colonies, mimicking a practice referred to as microbial transfer therapy in human medical settings[169]. Once a potent probiotic is identified, metabolic modelling can be used to predict the underlying prebiotic (that is, metabolite) to enable targeted microbiome manipulation through precision prebiotics[170]. Natural processes, such as the dispersion of microorganisms through trophic interactions[171], could also be leveraged to rehabilitate microbiomes. Even though microbiome restoration and rehabilitation is commonly centred around the use of environmental bacterial isolates, they are still perceived as drastic measures as they alter natural relationships[159]. We have to acknowledge that microbiomes in some systems may already differ from any pre-anthropogenic state (and be further changing following continuous environmental alteration). As such, our perception and definition of 'pristine states' are likely to represent an already altered and derived condition. Rehabilitating microbiomes of degraded ecosystems and disturbed organisms (that is, microbiome stewardship) represents one approach to marine ecosystem and organismal rescue to mitigate changed microbial relationships[159]. Conversely, the microbiome rewilding hypothesis posits that exposure to naturalistic environments can modulate or augment microbiomes and improve host–microorganism symbioses[172].

The complexity of the ecological interactions within the coral holobiont provides the foundation for a highly customizable and multifaceted approach for the use of microbiome interventions. Specifically, the assemblage and selection of bacteria can be tailored to a specific geographic location, threat or coral host; can be administered and altered (optimized with regard to changing needs) over time; or can be used in a preventive or remedial manner and applied before, during or after episodes of anticipated stress. A common critique is that microbial communities tend to restructure, returning to a state similar to the original[18,173]. This characteristic is typically viewed as a favourable outcome when applying probiotics in other hosts[174], as it highlights the dynamic nature of host–microbiome interactions and the benignity of the approach. Thus, although probiotics administered to corals were only retained temporarily or failed to colonize the host in previous studies[18,140], the application of probiotics may still promote a beneficial restructuring of the coral microbiome through altered organismal interactions and microbial successions[18], which may represent a rehabilitated state[159] (Fig. 3).

Challenges and directions for research

We still have a limited understanding of how long-term microbiome adjustments under climate change will affect coral holobiont biology. Comparative long-term monitoring at sites differentially affected by climate change may provide insight into microbiome adaptations and functional consequences[74,175]. In addition, we have identified three major research challenges to be addressed to fast-track our understanding of the microbial determinants sustaining coral health. The first challenge is to develop new methodologies and standardization for sequencing approaches (that is, metagenomics and metatranscriptomics) to reduce the proportion of eukaryotic contamination (that is, coral host, Symbiodiniaceae), which continues to dominate sequencing outputs and reduce their values[176]; to normalize sample preservation practices during field collection and downstream extractions of nucleic acids[176,177]; to target microhabitats within corals at scales that are relevant to the ecology and activity of the microorganisms and holobiont (as opposed to scales that are convenient to sample)[73]; and to establish reference databases tailored to coral microbiomes to improve their taxonomic and functional annotations and foster data integration across studies[178]. The second challenge is to characterize overlooked interactions, which will enable the identification of novel symbioses within the coral holobiont by pinpointing who interacts with who (for example, using metabolic interaction networks leveraging multi-omics data sets); and to determine the ecological linkages between the coral microbiome and other reef organisms or processes, expanding the roles that the coral microbiome has in coral reef ecosystems at large. The last challenge is to validate hypotheses generated through omics approaches by isolating and culturing a larger diversity of coral-associated bacteria using the full range of techniques currently available[20]; and by expanding the use of model systems to test the function and contribution of individual and groups of bacteria using co-culture approaches (that is, with axenic Symbiodiniaceae, antibiotic-treated Aiptasia and, ultimately, corals)[150].

The lack of cultured microorganisms and functional data hampers the identification, testing and mechanistic characterization of putative beneficial microorganisms for corals[117]. High-throughput and/or in situ microbial culturing[20] and the use of artificial intelligence-based approaches could overcome current limitations to accelerate and optimize screening processes for the identification of beneficial bacteria in vivo and in silico[179]. It is equally important to investigate key mechanisms and molecular cues underlying their (long-term) association. Once putative beneficial microorganisms for corals are cultured and characterized, the next challenge is their validation as effective probiotics. Such validation must follow well-monitored, standardized approaches comparing the efficacy against inert negative controls, excluding any confounding results[180]. The combination of different active interventions to increase coral resilience (for example, environmental hardening combined with probiotic provisioning) and their specific regimens required to achieve the beneficial outcomes are unknown[14]. The current challenges are intrinsically connected to the need for long-term monitoring to understand the duration of microbiome intervention effects[74].

In the absence of an established (legal) framework, microbiome-targeted interventions should be guided by clear environmental safety considerations, whereby the toll of inaction should be part of the risk assessment[13]. An evidence-based framework has been recently proposed to provide a path for implementing probiotics for wildlife, including corals[13], whereby an initial environmental diagnosis is followed by selection of native, non-pathogenic coral bacteria that are tested and monitored for any unexpected off-target effects. Although the One Health concept implies that healthy corals will contribute to a healthier reef[159], the effects of coral microbiome interventions on non-target organisms and the reef ecosystem are yet to be determined.

We anticipate the future of microbial therapies to be aimed at increasing coral resilience towards acute environmental challenges (for example, heat waves and disease outbreaks)[140], which will assist their survival and recovery. Understanding the underlying mechanisms is complex and can be either due to direct effects such as triggering immune responses or initiating epigenetic changes to achieve lasting altered states or due to indirect effects including altering microbial succession or nutrient assimilation. The use of microbiome intervention at scale is, at its core, an engineering problem that can benefit from technologies used in aquaculture, agriculture and bioremediation[31,181]. Coral probiotics may indeed have a major role (near term) in coral aquaculture, which will grow substantially to supply corals for field-based

restoration activities and follow similar approaches to those in other animal production systems that use aquaculture[147].

Conclusions and future perspectives

Reef-building corals are some of the most complex symbiotic systems to study, as each colony harbours hundreds of microeukaryotic and archaeal species, and thousands of bacterial and viral species. These communities are dynamic and vary within and between individual colonies, space and time. In this context, elucidating the contribution of individual microorganisms has been challenging. In other systems underpinned by complex symbioses, such as terrestrial plants, decades of research on microbiome functions now enable the engineering of plant–microorganism interactions to enhance the growth and productivity of specific species[182] and may soon enable greater carbon sequestration, or resistance to drought, pollutants or salts[183]. From a research point of view, harnessing bacterial metabolic repertoires to help 'future proofing' corals will therefore be reliant on our ability to improve our functional comprehension of coral–microorganism interactions.

Coral reefs are no longer pristine ecosystems, as decades to centuries of anthropogenic influences have substantially altered reef assemblages worldwide[184]. Current CO_2 emissions indicate that the global community will fail to limit warming to 1.5 °C above pre-industrial temperatures by 2100, with the most plausible scenarios projecting between 2 °C and 3 °C of warming[185]. This means that without rapidly reducing emissions to constrain warming below 2 °C, we are at risk of losing 99% of the world's coral reefs[186]. Importantly, addressing the root drivers of climate change and becoming carbon neutral as soon as possible underpin all other actions to avoid the ecological collapse of coral reefs[187]. As time is running out, it is therefore important to simultaneously accelerate our understanding of the role that bacteria have in coral health and develop approaches that can be used for active intervention[14]. Although microbiome-targeted interventions in laboratory settings can protect the host and promote its recovery following thermal stress[18], the efficacy of these approaches has to be evaluated in situ, and new methods are needed to deliver specific bacterial consortia at scale. Although the challenges are many and clearly identified, technological advances abound. Functional and mechanistic studies, manipulative experiments and evolutionary assessments of bacterial–coral relationships are not only possible but already underway. These efforts will be needed to safeguard the ecosystem functions and services provided by coral reefs.

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Author contributions

C.R.V., R.S.P. and J.-B.R. researched data for the article, substantially contributed to discussion of content, wrote the article, and reviewed and edited the manuscript before submission. D.G.B. substantially contributed to discussion of content, and reviewed and edited the manuscript before submission. A.C., C.P., H.L., A.R.M., S.A.A. and C.B.S. researched data for the article, wrote the article, and reviewed and edited the manuscript before submission. C.R.V. conceived and, with M.D., designed the figures. M.D. illustrated the draft figures, wrote the article, and reviewed and edited the manuscript before submission.

Competing interests

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