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Microbiome Engineering: A Promising Approach to Improve Coral Health

Jie Li [a,b,#,*], Qingsong Yang [a,b,#], Junde Dong [a,b,c], Michael Sweet [d], Ying Zhang [a], Cong Liu [a], Yanying Zhang [e], Xiaoyu Tang [a], Wenqian Zhang [a], Si Zhang [a,b,*]

[a] *CAS Key Laboratory of Tropical Marine Bio-resources and Ecology, South China Sea Institute of Oceanology, Chinese Academy of Sciences, Guangzhou 510301, China*
[b] *Southern Marine Science and Engineering Guangdong Laboratory (Guangzhou), Guangzhou 511458, China*
[c] *Tropical Marine Biological Research Station in Hainan, Chinese Academy of Sciences & Key Laboratory of Tropical Marine Biotechnology of Hainan Province, Sanya Institute of Ocean Eco-Environmental Engineering, Sanya 572000, China*
[d] *Aquatic Research Facility, Environmental Sustainability Research Centre, University of Derby, Derby DE22 1GB, UK*
[e] *School of Ocean, Yantai University, Yantai 264005, China*

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ABSTRACT

The world's coral reefs are threatened by the cumulative impacts of global climate change and local stressors. Driven largely by a desire to understand the interactions between corals and their symbiotic microorganisms, and to use this knowledge to eventually improve coral health, interest in coral microbiology and the coral microbiome has increased in recent years. In this review, we summarize the role of the coral microbiome in maintaining a healthy metaorganism by providing nutrients, support for growth and development, protection against pathogens, and mitigation of environmental stressors. We explore the concept of coral microbiome engineering, that is, precise and controlled manipulation of the coral microbiome to aid and enhance coral resilience and tolerance in the changing oceans. Although coral microbiome engineering is clearly in its infancy, several recent breakthroughs indicate that such engineering is an effective tool for restoration and preservation of these valuable ecosystems. To assist with identifying future research targets, we have reviewed the common principles of microbiome engineering and its applications in improving human health and agricultural productivity, drawing parallels to where coral microbiome engineering can advance in the not-too-distant future. Finally, we end by discussing the challenges faced by researchers and practitioners in the application of microbiome engineering in coral reefs and provide recommendations for future work.

1. Introduction

Coral reefs are the largest structures made by living creatures and are home to more than a quarter of marine life [1,2]. However, coral reefs on a global scale have been declining, a result of both local and global anthropogenic stressors [3–5]. Coral reef restoration (from passive rehabilitation to active human intervention) has received extensive attention in recent years as one way of trying to mitigate for this loss. Despite this attention, these practices still confront many theoretical and practical challenges [6].

The health of any given animal or plant is tied to their associated microbiota. Reef-building corals are thought to be associated with one of the most abundant and diverse microbiomes studied to date, including the corals' photosynthetic algal partners (the Symbiodiniaceae) as well as numerous bacteria, fungi, archaea, viruses, and protists [7,8]. The Symbiodiniaceae, which fix carbon and provide photosynthates to the coral host, are probably the most well studied members of the coral microbiome. However, the many other microbial symbionts also play essential roles across various biological processes and are therefore critical to host fitness and survival [9–12]. The association between corals and their microbiome provides flexibility for adapting to altered environments [13]. This flexibility allows the host to acquire new traits by restructuring its microbial symbionts. It may even facilitate the coral host in acclimating to new and changing environmental conditions, that is, the coral probiotics hypothesis [14]. If this happens naturally, then manipulation of the coral microbiome would allow for the enhancement of host fitness and improve tolerance and resilience in corals, offering a key tool for coral reef restoration practitioners [15–17]. This approach, called "microbiome

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[*] Corresponding authors.
E-mail addresses: lijietaren@scsio.ac.cn (J. Li), zhsimd@scsio.ac.cn (S. Zhang).
[#] These authors contributed equally to this work.

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engineering" is a mature science in other fields [18,19]. Indeed, microbiome engineering has been widely applied in improving human health and agricultural productivity [20].

2. Status of coral reefs

2.1. Rainforests of the sea

Coral reefs are sometimes referred to as the "rainforests of the sea," due to their high biodiversity and primary productivity [21]. Coral reefs occur mainly in tropical and subtropical shallow waters between 30° N and 30° S, especially in the Indo–Pacific and Atlantic–Caribbean regions. The total area of global coral reefs is estimated to be 2.8×10^5–6.0×10^5 km^2 [22,23]. Although coral reefs account for less than 0.1% of the world's seafloor, they support approximately 830 000 multicellular species and provide habitats for over 25% of marine organisms [24,25]. Coral reefs provide a range of services, including the provision of renewable resources (e.g., fisheries, materials for medicines, and algae), tourism, and coastal protection [26,27]. Although putting an economic value on such important ecosystems is difficult, many have attempted to do so. A value of more than 2 000 000 $\mathrm{USD \cdot ha^{-1} \cdot a^{-1}}$ has been proposed. Incidentally, this is much higher than all the rainforests and the rest of the open seas [28].

2.2. Threats to coral reefs

Despite their acknowledged importance, coral reefs are declining on a global scale at alarming rates. Before the first mass coral bleaching event occurred in 1998, global coral cover was thought to be around 30%. Approximately 8% of the world's coral reefs were lost because of that 1998 bleaching event. A further 14%, which is more than all the corals currently existing in Australia, has succumbed to various stress events between 2009 and 2018 [29]. Many now believe that all coral reefs may disappear by 2070 if climate change continues at the current rate [30].

Global climate change has led to a significant decrease of corals cover across different ocean regions all over the world [21]. Coral bleaching caused by ocean warming is regarded as the main reason for global coral reef deterioration [25]. In addition to bleaching, coral diseases (e.g., stony coral tissue loss disease (SCTLD)) are also now acknowledged as being equally, if not more disastrous, to the health of the global coral reef system [31,32]. Thermal stress also disrupts healthy competition between corals and other organisms [33,34]. This results in a phase shift, whereby coral reefs switch to macroalgae-dominant ecosystems, which limits recovery to the undisturbed states [35]. Ocean acidification is also documented to have negative impacts on coral reefs, including a reduction in the overall calcification rate, alterations in species interactions, and impairment of population replenishment, albeit at a slower rate [36,37]. Compromised calcification caused by ocean acidification impairs the capacity of corals to build their skeletons and makes corals more susceptible to disturbances and less resilient to damage [25,38].

However, the threats are not only from a global climate change. Local pressures, such as unmanaged coastal development, pollution, or overfishing, push coral reefs into states of reduced biodiversity, decrease coral coverage, and decrease ecosystem services [39]. In China for example, coral abundance on the fringing reefs has declined by over 80% due primarily to coastal development over just the past thirty years [40]. Pollutants from various land-based sources often cause eutrophication and stimulate phytoplankton and macroalgae blooms, thus slowing coral growth and reducing species richness [41]. Sedimentation from terrestrial runoff and dredging can affect corals directly through physical damage by abrasion and indirectly through a reduction in light availability due to increased turbidity [42]. Overfishing has resulted in the reduction of diversity and biomass of key functional species, such as top predators and herbivores [43]. Activities associated with coastal development, such as shoreline modification, and the growth of recreational and tourism-related activities also cause negative effects on coral reefs in many areas [44].

2.3. Restoring coral reefs

Coral reef restoration methods are undergoing rapid development. They include a range of techniques from passive restoration (i.e., reducing or excluding anthropogenic impacts) to active restoration (i.e., artificial intervention) [45]. Direct transplantation of coral fragments was the earliest method for "rescuing" degraded coral reefs [46,47]. Given the low cost and simplicity of this method, it has been adopted by approximately 20% of recovery projects [48]. The other traditional method, coral gardening, was first introduced in 1995 to culture asexual (fragments and colonies) and sexual recruits (or planula larvae) for further transplantation [49]. Currently, coral gardening has many variants depending on the stage of rearing and has become one of the most frequently used coral restoration methods [48].

In addition to the above two more "traditional" methods, a variety of larval enhancement methods that intervene in spawning, fertilization, and settlement processes have been developed to improve larval survival, a major bottleneck of coral reef restoration practices [50,51]. These methods include spawning induction [52], artificial spawning hotpots [53], assisted fertilization [54], cross-fertilization [55], larval cradles [56], and larval seeding [57]. The idea of assisted evolutionary approaches, which entails the inoculation of tolerant symbiotic microbial communities and Symbiodiniaceae in the early coral stages, was proposed to promote coral adaptability to environmental stress [58]. This draws attention to the fact that symbiotic microbes are also critical for coral resilience and adaptation in coral reef restoration [59,60]. Microbial approaches to restore corals have shown initial success in laboratory experiments [61–63] but remain to be explored in field restoration applications.

3. Microbiome and coral health

3.1. Coral microbiome

Reef-building corals are a good example of what has been called a "holobiont" or "metaorganism." These terms encompass the host (in this case the coral animal) and its microbial associates (protists, including the corals endosymbiotic microalgae, bacteria, archaea, fungi, and viruses [7,8]). Microorganisms have been found to be distributed across all the known "compartments" within the coral, including the calcium carbonate skeleton, tissue, gastrovascular cavity, and surface mucus layer (as shown in Fig. 1), with densities in order of magnitudes of about 10^9 $\mathrm{cells \cdot mL^{-1}}$ [64–67]. Since the culture-independent technique was first successfully applied to describe coral-associated microbial communities by Rohwer et al. [68], the coral microbiome has been extensively investigated. The microbial community structures in corals can vary with both physicochemical parameters of seawater and the inner microenvironment in coral hosts [7], which varies with host species [69], health state [70,71], life stage/age [72,73], and living conditions, including season [74,75], geographical position [76], ocean acidification [77], temperature [78], nutrients [79], and light [80]. There are now several theories or hypotheses that point to how the microbiome in its collective form assists its host and how engineering this part of the holobiont could be used in management and mitigation practices aimed at restoring or reviving coral reefs. These include the coral probiotics hypothesis [14], the

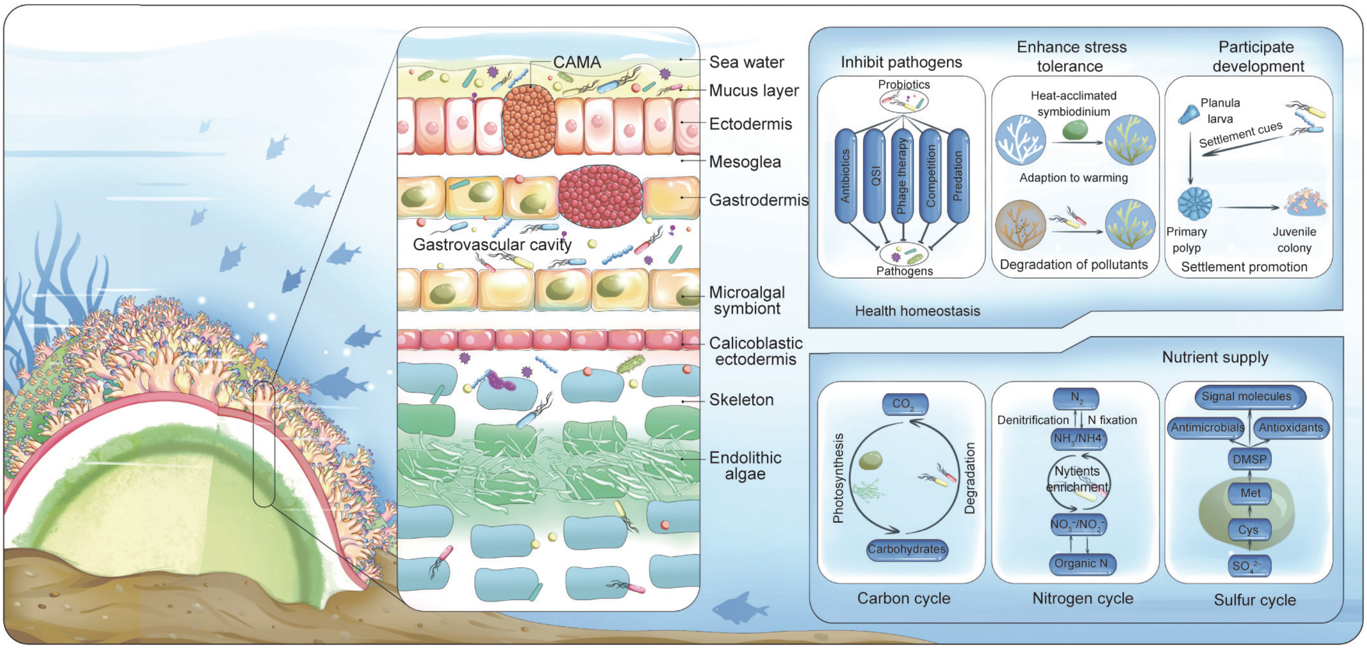

Fig. 1. Distribution and functions of the microbiome in the coral holobiont. CAMA: coral-associated microbial aggregates; QSI: quorum sensing inhibitor; DMSP: dimethylsulfoniopropionate.

host–microbe coevolution hypothesis [81], and the coral hologenome hypothesis [82]. Most researchers recognize that many microbial associates supply the host with additional nutrients and offer a level of immune defense such as antimicrobial production.

3.2. Nutrient cycles mediated by the coral microbiome

Carbon cycles mediated by the Symbiodiniaceae are fundamental to the coral reef ecosystem (Fig. 1) [83]. Harbored in the gastrodermis of the coral tissue, Symbiodiniaceae transfer fixed carbon to the coral host in the form of glucose, glycerol, and amino acids, which provide the coral holobiont with most of its energy requirements [64,84,85]. Other endolithic algae, dominated by the green algae *Ostreobium*, often present within the inner skeleton, also contribute significantly to the high primary productivity of coral reefs by supplying alternative sources of photosynthate [86]. They are particularly important when corals undergo bleaching [87].

In oligotrophic nitrogen-limited waters, biological nitrogen fixation is important for maintaining coral reefs. Nitrogen fixation by diazotrophs in the coral host has been shown to provide an essential source of new nitrogen to coral reef ecosystems [88,89]. There is evidence that the complete nitrogen cycle can be mediated by the coral microbiome alone, including nitrogen fixation, nitrification, denitrification, and anaerobic ammonium oxidation [90–92]. The high concentration of inorganic nitrogen within coral skeleton pores suggests that microbes in corals can accumulate and recycle nitrogen nutrients efficiently [93].

Sulfur is also an important nutrient, essential for the normal growth of coral holobionts. Though sulfur cycling in corals is poorly described, Symbiodiniaceae and several bacterial groups play important roles in the sulfur cycle of coral holobionts [59,94]. Dimethyl sulfate compounds (DSCs), produced mainly by Symbiodiniaceae, function in the antioxidant systems of coral [95]. Additionally, dimethylsulfoniopropionate (DMSP) was found to be a sign of the pathogen *Vibrio coralliilyticus* (*V. coralliilyticus*) in infecting heat-stressed corals [96]. The DMSP-degrading bacterial groups are capable of DMSP catabolism, which may restrict pathogenic infection [94,97].

3.3. Microbiome contributes to the coral health homeostasis

Through multiple mechanisms, including the mitigation of toxic compounds, niche competition with exogenous microorganisms, antagonism against pathogens, and adaptation to environmental shifts, microbes in coral hosts play important roles (Fig. 1) in host resilience and ensuring a healthy homeostasis [97]. In recent years, researchers have shown that the toxic impact of organic pollutants such as oil can be reduced by microbial degradation [98]. Coral-associated microbes have been shown to produce antibiotics and quorum sensing inhibitors (QSIs), which can inhibit the growth and virulence of pathogens [99,100]. We also know that the coral microbiome shifts and changes its composition when faced with stressors (either medium or long term) such as tidal fluxes, marine heatwaves, and ocean acidification [77,101,102]. Such rapid adaptive response has been linked to increasing the corals' resilience to repeated environmental stressors [103,104]. The microbiome has also been reported to be involved in coral larvae development by producing cues to promote coral larvae settlement and metamorphosis [105–109].

Although the functions of the coral microbiome have been extensively studied in recent years with advanced technologies such as high-throughput sequencing and nanoscale secondary ion mass spectrometry (NanoSIMS), we still have a long way to go in comprehensively understanding their functional mechanisms. Though the co-evolution of coral hosts and the microbiome is thought to assist coral adaptation to climate change and environmental degradation [81], more evidence from investigations over long time scales is needed. In addition, basic studies uncovering the functional mechanisms of the coral microbiome would provide additional concepts and solutions in microbiome engineering technologies that enhance coral tolerance.

4. Microbiome engineering and its applications

4.1. Common principles in microbiome engineering

Microbiome engineering is an experimental method that improves host fitness with designed microbial communities [19].

In practice, the common tools and approaches of microbiome engineering usually include chemical-based (prebiotics and antibiotics), cellular-based (probiotics and microbiota transplants), phage-based (bacteriophages), and host-mediated approaches [110,111]. The application of microbiome engineering can modify the composition of microorganisms and promote the development of ecological balance [20].

To promote the process of microbiome engineering, the iterative cycle of design–build–test–learn (DBTL) has been applied to microbial community construction and the development of technology [112]. The DBTL cycle starts at the **design** stage, in which strategies could be set at cellular level. Usually, there are two design processes: top-down (from inoculum selection to community selection) and bottom-up (from isolate selection to pathway optimization) [18,113]. At the **build** stage, the desired bacterial strains and pathways are produced through engineering, which usually includes synthetic and self-assembled construction methods [18,113]. The advancement of automation, genetic technologies, and individual designs used in the step of building can accelerate the systematic building of artificial microbiomes [18]. During the next **test** stage, emerging tools are used to evaluate microbiome function and determine the effect of the design–build plan [18,113]. Multi-omic approaches (such as meta-genomics, meta-transcriptomics, meta-proteomics, and meta-bolomics) can help us to fully understand microbial community dynamics, and interkingdom networking, for example, from the perspective of gene composition and gene expression information across time and space [114–118]. Multiplexed fluorescence spectral imaging and sequencing can illustrate the high-resolution analysis of microscale organization and provide insights into physiological functions and microbiome–host interactions [119–121]. Isotope tracing technology has also been used to measure the metabolic flux of the microbiome through time and space [122,123]. This can then be used in combination with metabolomics, metaproteomics, and physiological experiments to quantify the metabolic processes of the microbiome. In the final stage, our microbiome engineering process **learns** from the past. In this step we analyze and compare the collected data to help refine the cellular design for the next iterative cycle [113]. To reach a precise synthetic community design, mathematical modeling and computational analysis are also recommended [124]. Currently, one of the common mathematical models for the research of synthetic microbial communities is the generalized Lotka–Volterra model (LV), which is used to describe the abundance of different species over time [125–128]. To make a precise prediction for the social interactions in microbial communities, a set of unstructured kinetic models were employed to predict parasitism, commensalism, and cooperation among coexisting microbes [129]. There are overlaps and sub-iterations between the design, build, test, and learn stages [113] (Fig. 2) [18]. Interdisciplinary research teams with expertise in experimentation, computation, automation, and practice are essential for the DBTL approach, ensuring we can move forward in a logical manner and advance the development of microbiome engineering for any given host or ecosystem of interest [18].

4.2. The applications of microbiome engineering

The application of microbiome engineering in different fields, including biotechnology, medicine, agriculture, environmental bioremediation, and wastewater treatment, is becoming increasingly commonplace [130,131].

In humans, the microbes present in the gastrointestinal tract are known to play key roles in regulating human health [110,128]. By regulating the gut microbiome, the health of the host can be improved [110]. For example, the most blunt and dramatic means is via fecal microbiota transplantation (FMT). FMT has been successfully used in the treatment of *Clostridium difficile* infection (CDI), irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD) [132–134]. FMT is now being treated as an investigational new drug (IND) to treat CDI [135]. Other engineering modalities (e.g., administering a formulation of compounds and spores (prebiotics, probiotics, and synbiotics) and creating synthetic microorganisms (synthetic microbes)) that can potentially alter the microbiome have been used in animal model studies with beneficial effects on growth and disease treatment [20,136]. To date, most of these studies are restricted to model organisms. Controlled clinical trials are now required to evaluate the true effects and impacts on human health, over both the short and long term [20].

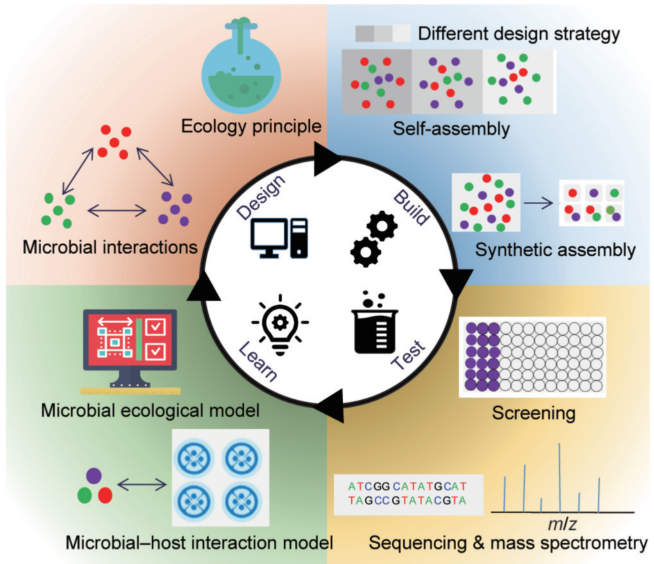

Fig. 2. The integrated DBTL cycles in microbiome engineering.

The strategies of microbial community modification (e.g., FMT, prebiotics, probiotics, antibiotics, phage therapy, clustered regularly interspaced short palindromic repeats (CRISPR), and CRISPR-associated proteins (CRISPR-Cas) [137]) have also been applied to animal livestock, farm animals, and aquaculture with beneficial effects on growth performance and immune responses commonly observed. Some of these trials and projects have already reached commercial platforms. For example, Immunogen® contains prebiotics of β-glucan and mannan oligosaccharide (MOS) to promote healthy immune function in fish from the family Cyprinidae [138].

Host-mediated microbiome engineering, microbiome breeding and transplantation, artificial microbial consortia, and soil additives (e.g., new organic soil amendments and root exudates) have been employed to engineer the root-associated microbiome with the aim of promoting plant growth or controlling agricultural pathogens [139]. This application of engineering the plant microbiome has had limited success due to the availability of functional native culturable microbes, the difficulty of establishing these cultures in a complex farm environment, and limited knowledge of stress-associated metabolism [140,141].

Microbiome engineering has also been applied in wastewater treatment by remediating contaminated groundwater with natural bacterial communities [142] and recovering wastewater by building reactor microbiomes [143]. This latter application is driven by an increased understanding of the roles of various microbial members, including the importance of protozoan predation in microbiome structuring [144]. In other similar artificial environments (pipelines, buildings, and ship hulls), microbiome engineering has been applied to remove specific species or strains deemed to have harmful properties (e.g., fouling organisms), while simultaneously enriching strains with more desirable properties (e.g., anticorrosion, antifouling, and self-healing of materials) [110].

Regardless of the target system, advancements in the fundamental aspects of research associated with microbiology and development of the technology around the DBTL cycle has promoted the progress of microbiome engineering. However, there are gaps in our knowledge that still hamper our progress. For example, our current understanding of the molecular and ecological mechanisms of many microbial communities (such as constructing a controllable and stable microbial interaction network and precisely characterizing and controlling the spatial structure of microbial communities and functions) remains limited. Being able to completely control environmental factors and thus the development and growth of key microbial groups, combined with the comprehensive use of modern multi-omics technology, will certainly facilitate our understanding of the functions of these microorganisms [131]. Once a stable microbiome engineering approach has been developed, we will be better placed to predict impacts and apply the "product" in a safe and controlled manner [145].

5. Engineering the microbiome to improve coral health

Microbiome engineering in corals has recently progressed from theory [14,59] to practice [61,62]. It can be achieved through artificial selection in the host–microbiome association, inoculation of the host with beneficial microbes, genetic engineering of specific microbial strains, or a combination of these approaches [15,97]. Although the application of microbiome engineering in corals is still in its infancy, pioneering studies have shown that it could be a powerful tool for helping us mitigate the threats associated with disease, increase coral stress tolerance to pollutants, and enhance coral resilience in the face of ongoing climate change (as summarized in Table 1 [61,63,98,104,109,146–154]).

5.1. Increasing coral's nutrition supply

Corals obtain their nutrition via autotrophy and/or heterotrophy. The autotrophic process relies on the photosynthetic activity of the Symbiodiniaceae, which may provide up to 90% of the energy needed by stony coral [155]. Despite the clear importance of the Symbiodiniaceae, we know that some essential nutrients for growth, such as nitrogen, phosphorus, and amino acids, can not be provided by the symbiotic algae. These nutrients must be captured via the coral's food or dissolved compounds [156]. During times of bleaching, when the symbiotic algae are absent or significantly reduced, carbon can be assimilated via heterotrophic means [156]. It has been reported that heterotrophic carbon may meet 15%–35% of daily metabolic demand in healthy corals and up to 100% in bleached corals [156,157].

Some heterotrophic nutrients captured by coral polyps cannot be used directly by the coral animal itself and instead must be metabolized and converted by its microbial symbionts. For example, phosphorus is not scarce in the environment but is mostly unavailable due to its easy conversion to the immobile form by precipitation with metalation [158–160]. Phosphate-solubilizing bacteria (PSB) can help the host improve phosphorus availability by solubilizing insoluble phosphorus [161]. In addition, there are some diazotrophs (nitrogen-fixing bacteria and archaea) that can convert dinitrogen (N_2) into ammonium (NH_4^+) through nitrogenase [93]. This will obviously help the host alleviate nitrogen limitation and improve primary productivity.

With the advent of the coral probiotic hypothesis, researchers have been experimenting with the feasibility of this approach and have achieved some initial positive results. For example, Zhang et al. [63] found that a consortium of potentially beneficial bacteria consisting of potential diazotrophs and PSB enhanced the total energy of *Pocillopora damicornis (P. damicornis)* and significantly increased the relative abundance of other potentially beneficial bacteria. Similarly, coral health can also be improved by increasing the nutrition supply from the autotrophic pathway. For example, research conducted by Morgans et al. [146] found that the inoculation of Symbiodiniaceae probiotics (*Durusdinium trenchii* and *Cladocopium goreaui*) can ameliorate bleaching-related stress and mortality of corals exposed to 32 °C for short time periods (six days in this example). In addition to carbon, nitrogen, and phosphorus, other elements, including sulfur, iron, and vitamins, are important for coral nutrient cycling [97]. Therefore, in future studies, additional cultured microbes should be tested for their capabilities to provide nutrients, and then applied in an effective, safe, and stable way.

5.2. Counteracting coral pathogens

Since the 1980s, researchers have described more than 40 coral diseases, all characterized by changes in pigmentation of the coral tissue at lesion sites, the presence of bands or mats, and/or the loss of coral tissue [162]. Among these 40 or so named diseases, only a handful are particularly common, including black band disease, brown band syndrome, the white syndromes or band diseases (including stony coral tissue loss disease), and yellow-band disease [163]. The occurrence and spread of coral diseases are thought to be influenced by various factors, including changes in the environment, pathogen population dynamics, and the status of the coral host's immune system [163–165]. At present, management measures for coral disease mainly consist of establishing accurate forecasting programs and mitigating tissue injury associated with fishing activities and derelict gear [166,167], sustaining functionally diverse fish assemblages [168], reducing entry points for opportunistic coral pathogens [164], selective breeding of resistant coral, and manipulating the diseased coral microbiome [163]. Among these measures, microbiome manipulation is a new approach for coral disease control, showing good application potential based on some of the studies that are available so far.

With the successful application of phage therapy in other aquaculture systems, it has been proposed as a promising approach for treatment of coral disease [147]. The unique bacterial predator of vibrios, *Halobacteriovorax*, could eliminate the increase in *V. coralliilyticus* (known as a temperature-dependent pathogen of some corals) and prevent secondary blooms of other opportunistic strains [148,169,170]. When a consortium of beneficial bacteria was applied to colonies of *P. damicornis* with *V. coralliilyticus*, they survived better than those without the probiotic [61]. These studies indicate that it is possible to counteract the impact pathogens have on their host through the practice of microbiome engineering. The exact mechanisms associated with these probiotics is not well understood. However, it is likely via direct antagonistic activity (e.g., antibiotic and anti-toxin products), along with more indirect modes of action such as niche colonization and the interruption of communication signals between pathogens [163,171,172].

Quorum sensing (QS) is a good example of this signaling aspect. It is a universal and critical mechanism for communication between bacteria. Depending on cell density or number, bacteria produce self-induced signaling molecules to regulate the genes and behavior of the entire bacterial community. This is considered an important pathway associated with bacterial spore production, antibiotic synthesis, and virulence factors [173,174]. The application of QSI is considered to be an effective but experimental treatment for coral diseases [172,175]. Studies have shown that QSI-producing bacteria are widely distributed in various marine habitats, including seawater, sediment, and corals [176–178]. They

Table 1
Reported case studies across multiple strategies to improve coral health by microbial engineering.

Category	Purpose	Host species	Microbial agents	Manipulation approach	Effects/results	References
Nutrients provision	Improve host nutrient supply	*Pocillopora damicornis* (*P. damicornis*)	Diazotrophs and phosphate-solubilizing bacteria	Inoculate the potential beneficial microorganisms for corals (pBMCs) consortium to the aquariums every six days	Enhanced host gross energy reserves (protein, lipids, and carbohydrates) and increased the relative abundance of potentially beneficial bacteria	[63]
	Ameliorate symbionts lost in bleaching	*Acropora millepora*	*Durusdinium trenchii* and *Cladocopium goreaui*	Inoculate Symbiodiniaceae to the tank once every three days	Increased photosynthetic efficiency and decreased coral mortality	[146]
Pathogen and disease control	Phage therapy of coral disease	*Favia favus*	Phage BA3 and its host *Thalassomonas loyana*	Inject phage to the boxes contained disease and healthy coral colonies via a syringe	Inhibited the progression of the white plague-like disease and promoted the transmission to healthy corals	[147]
	Control pathogen with predators	*Montastraea cavernosa*	Coral pathogen *V. coralliilyticus* predators *Halobacteriovorax*	Scored with a file to mimic tissue damage and inoculated microbes in the beakers	Predator bacteria diminished the adverse effects of pathogens and maintained the normal coral microbiome	[148]
	Alleviate coral bleaching	*P. damicornis*	pBMC consortium or quorum sensing inhibition (furanone)	Inoculate the bleaching-induced bacteria (*V. corallilyticus* and mixed-*N*-acyl homoserine lactones (AHL) producers) and antagonistic microbial agents	Mitigated coral bleaching by maintaining a healthy coral microbiome	[61,149]
Environmental stress tolerance	Increase coral heat tolerance	*Pocillopora* sp. and *Porites* sp.	Coral tissues homogenates of heat-tolerant corals	Inoculate the homogenates of donor coral tissues to the heat-susceptible recipient	Recipients bleached at lower rates compared to the control groups when exposed to short-term heat stress	[104]
	Protect coral via microbial oil bioremediation	*Mussismilia harttii* and *Millepora alcicornis*	Oil-degrading bacteria, filamentous fungi, and yeast	Inoculate the oil-degradation microbes to the coral culture tanks with oil	Mitigated the effects of oil on coral and maintained the coral health	[98,150]
Participating coral development	Promote the attachment and/or metamorphosis of the coral larvae	*Acropora willisae*, *Acropora millepora*, *P. damicornis*, *Porites astreoides*, and *Leptastrea purpurea*	*Pseudolteromons* sp., *Thalassomonas* sp., *Marinebacter* sp., *Cytophaga* sp., *Roseivivax* sp., *Pseudovibrio* sp., *Acinetobacter* sp., *Microbulbifer* sp., and *Metabacillus* sp.	Inoculate coral larvae with bacterial strains	Improved the rate of attachment and/or metamorphosis of coral larvae	[109,151–154]

can be isolated and purified, and, when tested, studies have found them to inhibit the toxicity of some pathogens [178,179]. Furthermore, laboratory experiments have shown that when QSI was added to corals, bleaching caused by pathogenic QS mechanism could be significantly relieved [149].

5.3. Improving tolerance to environmental stress

The degradation of coral reefs is caused by many factors, but the impact from ocean warming is the primary threat. Thermal stress increases the production of reactive oxygen species (ROS) by Symbiodiniaceae. Excess intracellular ROS levels can damage the algal symbiont's photosynthetic machinery and inhibit its repair, which further results in interfering with the supply of fixed carbon to the holobiont [180,181]. Improving the tolerance of Symbiodiniaceae and/or removing excess ROS by microbiome engineering would therefore be an effective strategy in assisting corals in coping with ongoing ocean warming.

These methods have been explored in the laboratory and currently show great promise. For example, inoculation of corals with heat-acclimated Symbiodiniaceae and/or potential beneficial microorganisms for corals (pBMC) consortium characterized by catalase activity, high free radical scavenging ability, and other beneficial functions can alleviate temperature stresses and mitigate coral bleaching [61,182–184]. In addition, Doering et al. [104] recently introduced the concept of coral microbiome transplantation (CMT). They used fresh homogenate made from heat-tolerant coral donor tissues to inoculate conspecific heat-susceptible recipients. They found that coral recipients bleached at lower rates than the control group when exposed to short-term heat stress (34 °C). This CMT strategy bypasses the time-consuming processes of culturing and screening for beneficial bacteria from healthy donors. More importantly, it enables the transmission of the "unculturable" microbiome fraction [104]. However, the extent to which the manipulations conferred thermal tolerance to the coral host and the long-term stability of the introduced symbiosis remains to be explored further.

Environmental contaminants (e.g., oil spills, microplastics, and heavy metals) are also a major threat to corals. These contaminants have been shown to influence coral energetics, growth, feeding behavior, photosynthetic performance, energy expenditure, skeleton calcification, and even tissue bleaching and necrosis [185]. Traditionally, after a spill, dispersants were used to break down the oil. However, scientists have found that the dispersants caused more damage to the corals than the spill, so more cost-effective and less damaging degradation methods were needed [98]. Fragoso ados Santos et al. [98] applied microbiome engineering to tackle this issue. They constructed a bacterial consortium from the coral *Mussismilia harttii* to degrade water-soluble oil fractions. This bacterial consortium accelerated the degradation of petroleum hydrocarbons and subsequently minimized the negative impacts of oil exposure on coral health [98]. Another example is the application of a multi-domain consortium for bioremediation, which maintained the physiological integrity of the corals while resulting in a significant degradation of *n*-alkane and polycyclic aromatic hydrocarbon fractions [150].

5.4. Accelerating artificial reproduction

Microbiome engineering can not only be applied to coral adults, but also has great potential in coral larvae. Corals have R reproductive strategies, in which parents release a large amount of gametes, but only a few larvae are able to successfully develop into adults [186]. In the coral life cycle, larval attachment and metamorphosis are bottlenecks in the recruitment of new individuals. This process is affected by many factors, among which crustose coralline algae (CCA) and microorganisms play an important role [186,187]. A *Pseudoalteromonas* strain isolated from CCA significantly promoted the metamorphosis of *Acropora willisae* coral larvae, resulting in a metamorphosis rate that reached 51.5% [151]. Various bacteria from other genera, including *Marinebacter*, *Cytophaga*, *Thalassomonas*, *Roseivivax*, *Pseudovibrio*, *Acinetobacter*, *Microbulbifer*, and *Metabacillus* have also been reported to have the ability to induce the attachment and metamorphosis of coral larvae [109,152–154]. These studies hint at probiotics that can be used to microbiome engineer larval settlement and increase survivorship. Although few studies focusing on coral have indicated this as a possibility, much less a success, such a process is already widely used in the aquaculture industry. For example, probiotics have been added to the rearing environment of shrimp larvae, improving the survival rate, promoting larval metamorphosis, and reducing the quantity of pathogens such as vibrios within the cultures [188].

6. The way forward

Based on the significance of coral microbiome to coral health, current developments in coral microbiology, and the principles of microbiome engineering, we propose a technical flow for developing microbiome engineering to improve coral health (Fig. 3). The progress made so far is summarized above. Below we discuss the remaining challenges that need to be overcome.

6.1. Uncovering the role of the microbiome in coral fitness

Manipulating a coral microbiome does now appear to be possible. However, we face several challenges to completely understand the impact of this technique and if the process can be scaled up. The main issue faced by researchers in this field is untangling the

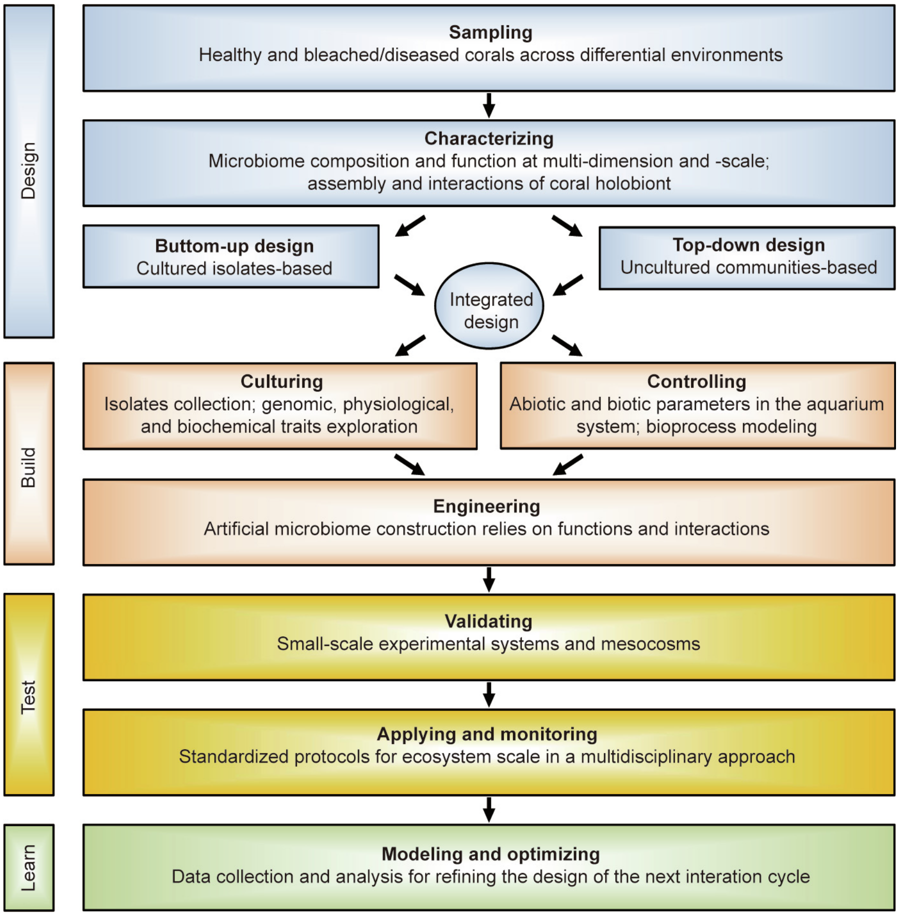

Fig. 3. Schematic of developing microbiome engineering to improve coral health.

complex interactions that come with the holobiont or metaorganism in its entirety. For example, currently we know a lot about the diversity of microbial symbionts at large spatial and temporal scales [9,13,102]. However, we know far less regarding changes at the micro-spatial and short-term time scales. Understanding the latter aspect is vital if we are to elucidate the mechanistic connections between the microbiome and their hosts within a multidimensional, multi-scale framework (Fig. 3). Additionally, our current understanding of *in situ* microbial activities and interactions within coral holobionts is extremely limited [189]. Nevertheless, the advancement of imaging technologies such as NanoSIMS, super-resolution microscopy, confocal Raman microspectroscopy, and single-cell and (meta)genomic/transcriptomic sequencing will inform this aspect in the not-too-distant future.

Further, while genomic approaches have undoubtedly provided us with in-depth insights into the molecular mechanisms employed by both coral hosts and their microbial symbionts, it is now critical to combine this genomic information with experimental evidence allowing for the confirmation of putative symbiont physiologies and functions in the holobionts. Additionally, the accumulation of coral genomes will be helpful to understand the role of the coral microbiome. Although microbial functions have been successfully evaluated through inoculating corals [61,62], it is imperative to establish axenic lines and mono- or poly-associated gnotobiotic animal models that will enable the testing of microbial functions and effects on coral fitness. Furthermore, testing the stability of the associations and the functions should be performed in both relatively short laboratory and long-term field experiments.

Since corals also interact with other living organisms, in addition to studying the relationship between the microbiome and coral hosts, understanding the relationships between interstitial associates and the coral microbiome will better facilitate coral restoration. Employing the interstitial associates, which are capable of promoting healthy microbiomes, may indirectly improve coral health. From this perspective, we should not overlook identifying the beneficial interactions caused by interstitial associates [190].

6.2. Identifying beneficial microorganisms for coral

Acquiring pure cultures is essential for BMC identification and microbiome manipulation (Fig. 3). Pure cultures are also necessary for phenotypic examination and the study of gene function through genetic manipulation [191]. For this reason, the development of approaches for isolating microbial taxa that are essential for coral functioning is crucial. However, compared with studies of coral-associated microbiomes using culture-independent molecular methods, the growth of coral-associated microbes in pure cultures has received less attention [191].

At present, BMCs are screened out by identifying the genes involved in nitrogen fixation (*nifH*), denitrification (*nirK*), DMSP degradation (*dmdA*), ROS scavenging potential, and antagonistic activity against coral pathogens [61,62]. If we can uncover more beneficial functions of various coral-associated microorganisms, this will be very helpful in screening for target strains that can improve coral health and fitness. The selection of candidates should use both qualitative and quantitative standards. A precise and quantitative selection approach will facilitate the optimization of microbiome engineering that can specifically modify the targeted host traits, such as heat tolerance, immune defense, or rapid growth. In addition to the small-scale tests, the beneficial characteristics of the microbiome must be verified in mesocosms, which ideally mimic field conditions as best as possible. This approach will ensure the results of the field application are properly validated. In each stage, it is essential to evaluate microbial colonization, effectiveness, repeatability, and mass application.

6.3. Application of beneficial microbiomes

Effectively delivering the pre- or probiotics is obviously a critical part of the application process of any microbiome engineering practice. This will also impact the scalability and therefore the cost of the process. Many current studies in small experimental systems inoculate the water column surrounding the corals or nubbins/colonies directly [61,62]. Application on the scale of a coral reef will face different challenges. Yet there are no studies that have tried and tested various possible solutions. Currently only concept papers have proposed possible large-scale techniques such as the immobilization or bioencapsulation of microbial cells [10,16]. Detailed testing of these delivery mechanisms needs to be performed in controlled laboratory settings that mimic the natural environment. Variables measured should include the impacts of water currents, the dilution effect, and how competition with indigenous micro- and macro-organisms will affect the probiotics' success.

The health of corals and reefs should be continuously monitored with standardized protocols before, during, and after any such microbiome manipulation trials [16]. This should be coupled with predefined indicators for each coral species within specific restoration projects (Fig. 3). While monitoring, it will also be necessary to acquire meta-omic datasets and assess outcomes at the ecosystem scale. Integrating the *in situ* abundance and activity of BMCs and the outcomes of BMCs inoculation could provide guidance for how often BMCs need to be re-inoculated. Further, specific microbial manipulation strategies must be customized according to the situation of the target coral reef or a certain coral species.

6.4. Integration of microbiome engineering into reef restoration

Integration of BMCs into the restoration of coral reefs, including environmental hardening, selective breeding, coral transplantation, and artificial reef setting, still needs to be examined to determine the most effective strategy (for example, using BMCs in coral nurseries and the formation of BMCs biofilms on the surface of artificial reefs). From the perspective of technology, the establishment and application of microbiome engineering in coral reef ecosystem restoration requires a multidisciplinary approach that involves resource microbiology, microbial ecology, microbial genetics, marine ecology, materials science, and ecological engineering. Furthermore, the application of microbiome engineering requires cooperation between the government, industry, and academia to form rational development, utilization, and management systems.

7. Conclusions

With unprecedented changes in coral reefs occurring in the current epoch, the requirements of effective conservation and restoration of corals are more compelling than ever. Microbiome engineering provides a powerful approach to improve coral health, although the field of coral microbiome engineering is in its infancy. Filling large knowledge gaps and finding an optimal method to implement this approach in a complex ecosystem are crucial for the successful development and application of microbiome engineering in coral reef restoration. Achievements in animal health and agriculture productivity could help guide the application of microbiome engineering in enhancing coral resistance and/or resilience to adverse environments. We propose that microbiome engineering is a promising approach for improving coral health and could facilitate resolving the coral reef crisis in combination with other restoration practices.

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Compliance with ethical guidelines

Jie Li, Qingsong Yang, Junde Dong, Michael Sweet, Ying Zhang, Cong Liu, Yanying Zhang, Xiaoyu Tang, Wenqian Zhang, and Si Zhang declare that they have no conflicts of interest or financial conflicts to disclose.

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