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Review

Metaorganisms in extreme environments: do microbes play a role in organismal adaptation?

Corinna Bang[a], Tal Dagan[a], Peter Deines[b], Nicole Dubilier[c], Wolfgang J. Duschl[d], Sebastian Fraune[b], Ute Hentschel[e], Heribert Hirt[f], Nils Hülter[a], Tim Lachnit[b], Devani Picazo[a], Lucia Pita[e], Claudia Pogoreutz[g], Nils Rädecker[g], Maged M. Saad[f], Ruth A. Schmitz[a], Hinrich Schulenburg[b], Christian R. Voolstra[g], Nancy Weiland-Bräuer[a], Maren Ziegler[g], Thomas C.G. Bosch[b,*]

[a] Institute of General Microbiology, Kiel University, Am Botanischen Garten 1-9, 24118 Kiel, Germany
[b] Zoological Institute, Kiel University, Am Botanischen Garten 1-9, 24118 Kiel, Germany
[c] Max Planck Institute for Marine Microbiology, Celsiusstraße 1, 28359 Bremen, Germany
[d] Institute of Theoretical Physics and Astrophysics, Kiel University, Leibnizstraße 15, 24098 Kiel, Germany
[e] GEOMAR Helmholtz Centre for Ocean Research, Wischhofstraße 1-3, 24148 Kiel, Germany
[f] Center for Desert Agriculture, Division of Biological and Environmental Science and Engineering, King Abdullah University of Science and Technology (KAUST), Thuwal 23955-6900, Saudi Arabia
[g] Red Sea Research Center, Division of Biological and Environmental Science and Engineering, King Abdullah University of Science and Technology (KAUST), Thuwal 23955-6900, Saudi Arabia

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ABSTRACT

From protists to humans, all animals and plants are inhabited by microbial organisms. There is an increasing appreciation that these resident microbes influence the fitness of their plant and animal hosts, ultimately forming a metaorganism consisting of a uni- or multicellular host and a community of associated microorganisms. Research on host–microbe interactions has become an emerging cross-disciplinary field. In both vertebrates and invertebrates a complex microbiome confers immunological, metabolic and behavioural benefits; conversely, its disturbance can contribute to the development of disease states. However, the molecular and cellular mechanisms controlling the interactions within a metaorganism are poorly understood and many key interactions between the associated organisms remain unknown. In this perspective article, we outline some of the issues in interspecies interactions and in particular address the question of how metaorganisms react and adapt to inputs from extreme environments such as deserts, the intertidal zone, oligothrophic seas, and hydrothermal vents.

1. All organisms are metaorganisms

Discovering that individuals are not solitary, homogenous entities but consist of complex communities of many species that likely evolved during billions of years of coexistence led to the «metaorganism» concept (Rosenberg et al., 2007; Zilber-Rosenberg and Rosenberg, 2008; Bosch and McFall-Ngai, 2011; McFall-Ngai et al., 2013; Theis et al., 2016; for the terminology see Table 1) which considers the dynamic communities of microorganisms on epithelial surfaces as an integral part of the functionality of the respective organism itself. Consequently, microbes are considered to be an essential part of the animal phenotype influencing the fitness and thus ecologically important traits of their hosts (McFall-Ngai, 2002; O'Hara and Shanahan, 2006; McFall-Ngai, 2007; Fraune and Bosch, 2010; Gilbert et al., 2012; Bordenstein and Theis, 2015; Deines et al., 2017) (Fig. 1).

The microbiome research of the last decades has revealed that in particular human and animal hosts can be associated with highly complex microbial consortia. The Human Microbiome Project in particular has shown the impact of host genetics, diet, or antibiotic treatment on the microbial diversity within the human gut (Lozupone et al., 2012; Goodrich et al., 2014; Blaser, 2016), while laboratory and preclinical tests suggest that several metabolic and neuronal disorders are linked to alterations in this diversity (Tremaroli and Bäckhed, 2012; Hsiao et al., 2013; Gilbert et al., 2016). Besides the human model, animal and plant models for host–microbe interactions exist that offer unique opportunities to address questions related to symbiosis and

* Corresponding author.
E-mail address: tbosch@zoologie.uni-kiel.de (T.C.G. Bosch).

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Table 1
Terminology.

Holobiont	A eukaryotic host with all its associated microbial partners. This multispecies assemblage includes viruses, phages, eubacteria, archaea, fungi and protozoa.
Hologenome	Genetic information encoded in the eukaryotic host and all of its associated partners. This collective genome forms the theoretical genetic repertoire of a holobiont (definition by Deines et al., 2017)
Metaorganism	Includes the function of a holobiont in a given environment. The function of a holobiont depends on (i) the presence and composition of the associated partners, framing the genetic potential of the holobiont, the hologenome; (ii) the activity, abundance and the transcriptionally active part of the genome of every single partner of the holobiont; (iii) this subsequently results in host–microbe and microbe–microbe interactions which must be kept in a state of homeostasis in order to maintain a stable holobiont. To emphasize this highly dynamic functional state (capacity) of a holobiont we will in the following use the term "metaorganism" (see also Deines et al., 2017).
Microbiome	Refers to an "ecological community of commensal, symbiotic, and pathogenic microorganisms within a given host" (Lederberg and McCray, 2001).

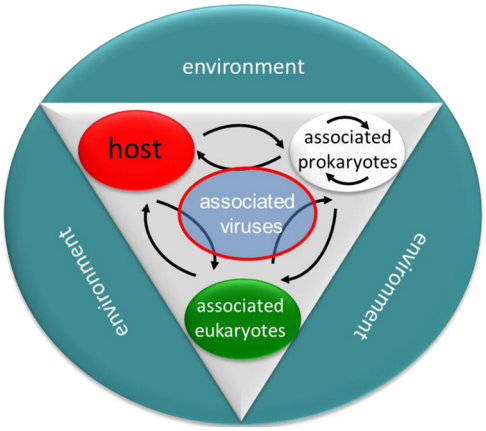

Fig. 1. Multicellular organisms are metaorganisms composed of the macroscopic host and synergistically interdependent bacteria, archaea, viruses, and numerous other microbial and eukaryotic species including fungi and algal symbionts. From Bosch (2013).

host–microbe interactions (Ruby, 2008; Bosch and McFall-Ngai, 2011; Kostic et al., 2013). Some years ago, Ruby (2008) already distinguished between artificial and natural model systems. Artificial laboratory models, such as flies (*Drosophila melanogaster*), worms (*Caenorhabditis elegans*), zebra fish or mice, allow the assessment of the influence of specific genetic or environmental factors on holobiont fitness. However, these laboratory models are highly derived and often lack the link to their original existence in nature. In contrast, natural models provide a relevant ecological and evolutionary framework; however, their experimental manipulation is typically limited and restricted to one host–one symbiont types of interactions (e.g., the squid *Euprymna scolopes* and the bacterium *Vibrio fisheri*), or to symbioses between animal hosts and low-diversity microbiota (e.g., *Hydra* sp. and some bacteria or *Arabidopsis* and the phyllosphere microbiome).

Extreme environments provide a particularly interesting natural context because of the specific challenges to maintain basic life functions under challenging conditions. Yet, due to the extremes in physico-chemical characteristics (temperature, pressure, salinity, light), but also the limited access and the problems of collection render experimental work with organisms from extreme environments difficult. In consequence, with a few noteworthy exceptions (e.g., deep-sea hydrothermal vents), we still know remarkably little about the biology of metaorganisms from these environments, while the available information from established experimental models is unlikely to be representative of these 'extremophile' metaorganisms. Additionally, the study of complex ("high-diversity") consortia, as they frequently occur in nature, remains challenging because multiple interactions take place simultaneously, making it difficult to decipher the specific roles of each symbiont in the community. Methodologies such as the establishment of gnotobiotic, germfree, or axenic hosts are still limited in many natural models, and symbionts are frequently recalcitrant to cultivation. Owing to new deep-sequencing technologies, the extent of diversity and function in highly complex systems is thus just beginning to be unraveled (McFall-Ngai et al., 2013). These omics-driven approaches in combination with meaningful functional assays promise to reveal new insights into the functional and mechanistic underpinnings of metaorganism biology in natural and extreme environments. Current research is focused on understanding the general principles by which these complex host–microbe communities function and evolve: which selective forces drive the evolution of these interactions, i.e. how do the associated organisms influence each other's fitness?

Life is found in almost all places on Earth under a multitude of different conditions, including extreme environments. These habitats are characterized by either extreme conditions in one (or more) abiotic parameter(s) or by parameters that greatly fluctuate during relatively short timespans. Some of the most challenging habitats are deserts (Ward, 2016), tidal zones with rapidly fluctuating physico-chemical parameters (Raffaelli and Hawkins, 1999), oligotrophic oceans (Miller and Wheeler, 2012), and the deep sea (Van Dover, 2000). Here we address the potential role of the associated microbial community in adapting a given host to extreme environments. We first describe the diverse ecological and evolutionary processes that shape the microbial community. We continue by discussing metabolic interactions and inter-species communication pathways in metaorganisms and their potential impact on living in extreme environments. We then highlight several examples of metaorganisms in extreme environments such as desert conditions, the intertidal zone, oligotrophic seas, and hydrothermal vents. We also throw some light on forgotten players such as viruses and archaea, and visit extreme conditions on terrestrial planets before summarizing how the associated microbiome can promote the host's vigour and proliferation under extreme conditions.

2. Understanding the adaptation to extreme environments requires an understanding of the evolutionary and ecological processes that shape the associated microbial community

Adaptation to extreme environments represents a particular challenge for any organism. The involved processes are usually studied by characterizing the genetic changes spreading through populations in response to natural selection or drift. Genetic adaptation of eukaryotic species is usually slow because new variants require several host generations to achieve marked frequencies in populations. A faster response can occur through phenotypic plasticity, and/or the reversible adjustment of individual phenotypes to environmental conditions. Such plastic responses can also be inherited when involving epigenetic change, such as alterations in DNA methylation patterns. The fastest responses may be mediated by associated microbes due to their significantly shorter generation time (Fig. 2). In particular, changes in the presence/absence of microbial species and strains and also in their relative proportions (i.e., ecological processes) can result from novel abiotic or biotic constraints. These ecological changes are likely able to effectively promote rapid adjustments of the entire metorganism's physiology and safeguard metabolic homeostasis of the host. Moreover, even single bacterial species can display extensive phenotypic variability/heterogeneity (Raj and van Oudenaarden, 2008) that can enhance resilience (Justice et al., 2008) to environmental changes and thus facilitate adaptation of the host.

Rapid adaptation can further occur through genetic changes at the

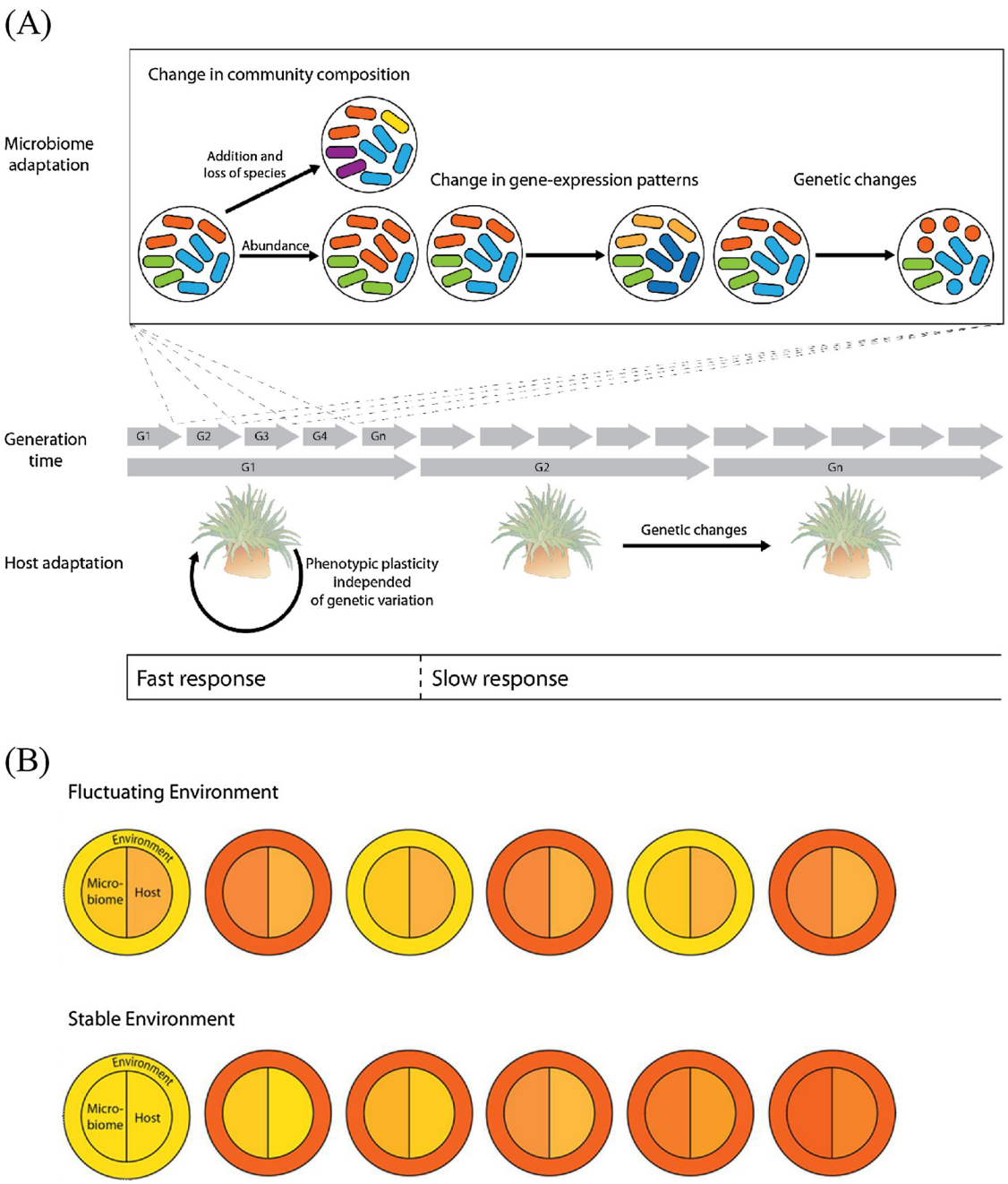

Fig. 2. Processes shaping the adaptation of metaorganisms to extreme environments. (A) Rapid adaptation is possible through ecological and genetic changes of the microbiome due to comparatively short generation times (and large population sizes), but also through phenotypic plasticity of the host. Slow responses involve genetic changes in the host. (B) Adaptation to fluctuating environments (changes between yellow and red in the outer circle) is mainly determined by changes in the microbiome, which adapts to each new environment faster than the host (indicated by the colour change of the microbiome). The change to a novel stable environment can be driven by initial adaptation of the microbiome (indicated by increases in red intensity) followed by subsequent adaptations of the host (modified from Soen, 2014).

level of individual bacterial cells. One particular phenomenon is phase variation (e.g., Van der Woude, 2011). Mediated mostly through intragenomic recombination processes (e.g., site-specific recombination, genomic rearrangements, etc.) and even epigenetic switches (e.g. Van der Woude, 2011; Li et al., 2016), phase variation comprises abrupt and distinct on/off-like phenotypic switches based on differential protein expression profiles in a reversible and irreversible manner. Moreover, bacterial adaptability is fueled by spontaneous mutations or intragenomic recombination (Harms et al., 2016).

Even though the proportion of beneficial mutations among neutral and detrimental mutations appears to be small (e.g., 2×10^{-9} per genome per replication for *E. coli*; Imhof and Schlötterer, 2001), the associated microbes are expected to adapt faster to changing environmental conditions than their hosts, due to their shorter generation times and their much greater population sizes (both relative to their hosts). The generation of genetic novelty might be facilitated by reversible mutator phenotypes within bacterial populations. Such mutators can arise spontaneously, often at higher frequencies than expected from the mutation/selection equilibrium, suggesting a selective advantage under specific conditions (Denamur and Matic, 2006), such as fluctuating environments (Travis and Travis, 2002). Furthermore, adaptation may also be enhanced by bacterial horizontal gene transfer (HGT), which is the exchange of genetic material, including mobile genetic elements (MGEs) such as plasmids, transposons, and phages. HGT events allow

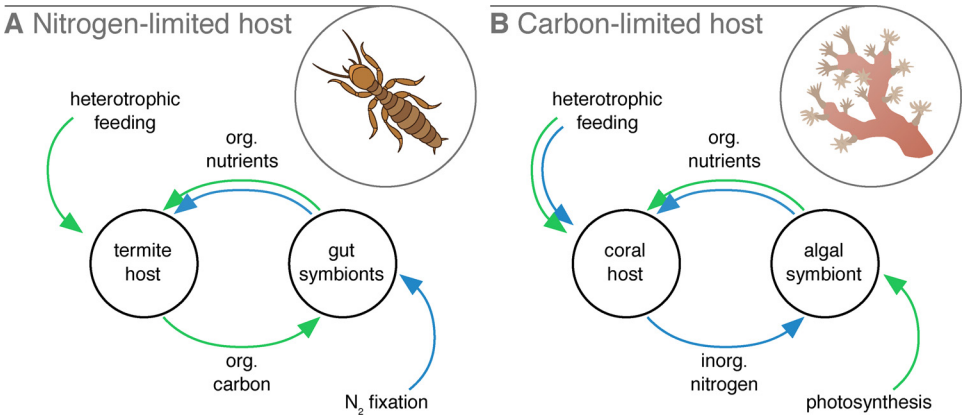

Fig. 3. Exemplary carbon (green) and nitrogen (blue) fluxes in (A) a termite metaorganism and (B) a coral metaorganism. In both cases the animal host is nutrient-limited, yet this limitation is attenuated or overcome due to nutrient exchange and/or nutrient recycling with/by microorganisms associated with the host.

rapid access to genetic innovations of non-parental lineages and contribute to the dissemination of beneficial mutations, especially between closely related species (Aminov, 2011). MGEs serve as indispensible vehicles promoting recombination during HGT, and their acquisition can, depending on the context-dependent beneficial genes which are carried, promote rapid adaptation. HGT shows high prevalence in, for example, the human gut microbiome (Smillie et al., 2011; Brito et al., 2016).

The potential of microbial communities to promote host evolution is additionally influenced by population genetic processes. In particular, genetic drift and population bottleneck events result in a reduction of the population size of specific microbiome members and thereby affect the adaptation of the metaorganism in different ways. Neutral changes in the microbial community composition due to drift could facilitate shifts in the occupation of ecological niches by newly incoming species. Severe fluctuations of environmental conditions could potentially eliminate standing genetic variation and low-fitness genotype variants within the host's microbiota. Thereby, species–species competition within the microbial community might be reduced and selective advantages conferred to better-adapted genotypes. Clonal interference, where lineages with different beneficial mutations coexist and compete in the population, is likely to positively affect the adaptability of the metaorganism by prolonging transient polymorphic population states with greater genetic diversity (Barroso-Batista et al., 2014).

In summary, understanding the adaptation to extreme environments requires an understanding of the diverse possible responses within the metaorganism (Fig. 1), especially the evolutionary and ecological processes that shape the associated microbial community (Fig. 2). The study of metaorganism evolution should thus be placed in a more general framework of species interactions where the unit of selection is defined by the lineages/populations of both host and microbes within the hierarchical structure of the metaorganism.

3. Metabolism and nutrient cycling in the metaorganism

Can microbes help hosts to perform well in extreme environments? The metabolic capacities encoded in metazoan genomes are in general limited to a narrow range of environmental conditions (Nursall, 1959; Pörtner, 2001). Yet, despite these limitations metazoan life is found even in the most extreme environments (Weber et al., 2007). Understanding how organisms manage to flourish in environments that exceed their own metabolic limitations requires the consideration of the entirety of metabolic processes of the metazoan host and its associated bacteria; in other words, the metaorganism rather than the individual (Bosch and McFall-Ngai, 2011) (Fig. 1). This is particularly apparent as the diversity of microbial metabolic processes by far exceeds those of their metazoan hosts. As a consequence, the metabolic capacity of metaorganisms is governed by the interactions of their individual members (McFall-Ngai et al., 2013). The emerging properties of the combined metabolism thus allow the metaorganism to flourish in environments otherwise uninhabitable for its individual members (McMullin et al., 2000). The nature of the associations supporting such metabolic interactions within metaorganisms can be highly diverse, ranging from parasitic (Kanaani and Ginsburg, 1989) through commensalistic (Hooper et al., 2001) to mutualistic (Douglas, 1998) associations, depending on whether nutrient limitation is increased, unaffected or attenuated by the symbiotic partners.

The importance of these host–microbe interactions for metaorganism performance and fitness is well documented by two illustrative examples:

(1) *The symbiosis between wood-feeding termites and their gut microbes.* The evolutionary success of wood- and litter-feeding termites is based on their ability to efficiently digest lignocellulose although it is highly recalcitrant to enzymatic attack and has a low nitrogen content (Abe et al., 2000). An intimate symbiosis with archaeal, bacterial, and eukaryotic gut microbes facilitates the breakdown and utilization of this otherwise inaccessible food source (Brune, 2014; Waidele et al., 2017) (Fig. 3A). Furthermore, the low nitrogen content of this diet is compensated by dinitrogen (N_2)-fixing bacteria which provide a critical source of organic nitrogen in an otherwise strictly nitrogen-limited system (French et al., 1976).

(2) *The symbiosis between tropical corals and their endosymbiotic algae.* Tropical reef-building corals flourish in highly oligotrophic waters with low food and nutrient availability (Gove et al., 2015). The productivity of these metaorganisms is supported by the association between corals and their endosymbiotic dinoflagellate algae (Muscatine and Porter, 1977). In this symbiosis, the algal symbionts translocate the majority of photosynthetically fixed carbon to the host, which in return provides inorganic nutrients, i.e. nitrogen derived from its metabolism, to the symbiont (Tremblay et al., 2012; Rädecker et al., 2015) (Fig. 3B). Given that neither heterotrophic feeding nor nutrient uptake from seawater can sustain the nutritional requirements of these symbiotic partners on their own, the recycling of nutrients within this symbiosis is fundamental to ensuring the survival and growth of the coral metaorganism (Muscatine and Porter, 1977; Tanaka et al., 2018).

In both examples, the mutualistic symbiosis between a carbon-limited (coral host, termite gut bacteria) and a nitrogen-limited (termite host, endosymbiotic algae) organism enables these metaorganisms to overcome their nutrient limitations. At the same time, these symbiotic interactions do not occur in isolation, but are part of a much more complex metabolic interaction network within the metaorganism that

ultimately provides sufficient nutrition to all its members. In this way, these metaorganisms could conquer new ecological niches, making them important ecosystem engineers of their respective environments (Jones et al., 2008).

Yet, these two types of nutrient-exchange symbioses represent two different strategies regarding their ecological maintenance and the regulation of nutrient transfer. In the case of the termites, the gut microbes process a food source which would otherwise be inaccessible for the host. Microbial biomass is excreted from the hindgut and re-ingested by the host, thereby completing the nutrient exchange between these partners (Brune, 2014). In this scenario, growth and fitness of the symbiotic partners are positively correlated, as the growth of one partner directly benefits the other (Shantz et al., 2015). In the case of corals, on the other hand, the nutrient exchange is facilitated by the constant nutrient-limited state of both symbiotic partners (Shantz et al., 2015). Here, the nitrogen derived from the host metabolism is insufficient to satisfy the nitrogen demand of the algal symbiont (Rädecker et al., 2015). Consequently, a large fraction of the photosynthetically fixed carbon cannot be converted into algal biomass as growth requires the availability of nitrogen (Cunning et al., 2017). The resulting accumulation and subsequent release of organic carbon is driving the translocation of carbon in this symbiosis (Cunning et al., 2017). At the same time, this carbon is insufficient to fully satisfy the carbon requirements of the coral host, resulting in the accumulation and release of inorganic nutrients and thereby completing the nutrient exchange to the benefit of both partners in this symbiosis (Rädecker et al., 2015; Cunning et al., 2017). Consequently, in this mode of regulation the disruption of the nutrient limitation of one symbiotic partner would pose a threat to its partner as it reduces the amount of nutrients available for translocation (Muller et al., 2009; Wooldridge, 2013). For example, Pogoreutz et al. (2017a) suggested that the stimulation of coral-associated N_2-fixing bacteria may disrupt the nitrogen limitation of the algal symbionts, ultimately resulting in the retention of photosynthates and the disruption of this symbiosis. Microbial N_2-fixation, therefore, may have potentially significant implications for coral resilience to environmental stress (Pogoreutz et al., 2017a,b). As a consequence, growth and fitness may be negatively correlated between the two partners in this mode of regulation (Cunning and Baker, 2012; Shantz et al., 2015).

Despite these fundamental differences (i.e., positive vs. negative correlation of metaorganism performance or fitness between host and symbiont), both types of nutrient exchange symbioses may ultimately increase the productivity and fitness of the overall metaorganism under stable environmental conditions (Muller et al., 2009; Hill and Hill, 2012). Under changing environmental conditions, however, especially symbioses with a negatively correlated fitness of the partners may be highly vulnerable as changes in the fitness of one of the two partners may destabilize the overall balance of the delicate symbiotic system (Shantz et al., 2015). For corals, the fragility of such symbioses is tragically documented in the form of coral bleaching, i.e. the loss of algal endosymbionts due to the disruption of the coral–algae symbiosis that has been repeatedly observed in recent years on a global scale due to ocean warming (Hughes et al., 2017, 2018).

While such instabilities of metabolic interactions within a metaorganism due to environmental changes may pose a serious threat to metaorganism functioning, rapid alterations in metabolic interactions may also aid in fast acclimatization/adaptation responses. Reshef et al. (2006) postulated that the environmental selection of optimal microbial communities within a metaorganism should result in highly adapted, beneficial microbiomes which may increase metaorganism fitness under these conditions. Indeed, such rapid microbiome restructuring can convey new metabolic traits which facilitate the metaorganism's adaptation and acclimatization to environmental changes (Moran and Yun, 2015; Ziegler et al., 2017). In corals, for example, heat-induced symbiont shuffling or strong environmental selection selects for novel communities of algal symbionts with increased heat tolerance and altered nutrient cycling properties, thereby ultimately improving the heat tolerance of the overall coral metaorganism (Baker et al., 2013; Silverstein et al., 2014; Hume et al., 2016). Hence, by being able to change their metabolic profiles through microbiome restructuring rather than having to rely on mutation and recombination alone, metaorganisms can rapidly respond to changing environmental conditions (Rosenberg and Zilber-Rosenberg, 2016).

Microbiome flexibility, however, may proof detrimental to the metaorganism if microbial metabolic processes become increasingly important for metaorganism functioning, due to the potential loss of critical symbionts and associated microbial functions (Bennett and Moran, 2015). Hence, redundancy of important microbial functional groups and/or strong regulation of important symbionts are important factors for maintaining metaorganism structure and function during environmental changes (Allison and Martiny, 2008; Wittebolle et al., 2009). However, the increased reliance on symbionts to fulfill critical metabolic functions may be accompanied by high rates of horizontal gene transfer between all members of these metaorganisms (Nikoh and Nakabachi, 2009; Bhattacharya et al., 2016). Via this mechanism, important functional metabolic traits may be transferred from one symbiotic partner to another, thereby reducing the dependence on individual symbionts, and ultimately increasing metaorganism stability (Raina et al., 2013; Bhattacharya et al., 2016). In highly obligate nutrient exchange symbioses such gene transfer and deletion ultimately lead to the degeneration of symbiont genomes (Moran, 2002). In isolated evolutionary events, this may even have resulted in the formation of new cell organelles, such as mitochondria and plastids, thereby disrupting our traditional understanding of organism identity and boundaries (Keeling and Palmer, 2008; Theis et al., 2016).

Taken together, the metabolism of metaorganisms is an emerging feature of all its members combined. The rapid acquisition and the flexibility of metabolic traits has enabled metaorganisms to conquer even the most extreme environments and environmental niches, and may also assist them in a time of anthropogenically driven environmental change.

4. Living in extreme environments requires extensive interspecies communication

Since the beginning of metazoan evolution, the development of multicellular organisms has depended on the association with bacterial communities (King, 2004). These associations are mediated by communicating with each other through various chemical compounds. This interkingdom cell-to-cell signaling involves small molecules such as hormones that are produced by eukaryotes and hormone-like small molecules that are produced by bacteria (Pacheco and Sperandio, 2009).

Bacterial cell-to-cell signaling, referred to as quorum sensing (QS), allows bacteria to coordinate gene expression within a population. QS is based on the synthesis and perception of autoinducers (AI), which either diffuse through the cytoplasmic membrane or are actively transported and specifically detected by a certain receptor. When the AI binds to its corresponding receptor, the subsequent signal transduction activates the transcription of target genes, often including those encoding the respective AI synthase (autoregulation) (Fuqua et al., 1994). When the population density increases, the concentration of the signaling molecule exceeds a certain threshold ("quorum"), thus causing more autoinducers to be synthesized through the induction of AI synthase. Activation of the receptor changes the regulation of target genes, leading to synchronized transcription in the population (Bassler, 2002). Thus, cell density-dependent behaviors are coordinated (for review see Castillo, 2015), e.g., colonization, biofilm formation, virulence, motility, bioluminescence and pathogenicity (Landini et al., 2010; Castillo-Juárez et al., 2015).

In a complex microbial community, such as a metaorganism, a large number of chemical "languages" are spoken. A single bacterium has to

selectively respond to certain “dialects”. As different bacterial species use QS to enhance their competitive advantages (Bassler, 2015), it is rational that competitors also have evolved mechanisms to interfere with the QS systems to prevail over the competition. The mechanisms causing the inactivation of QS systems are generally known as “quorum sensing interference” (QSI) or “quorum quenching” (QQ) (Kalia, 2015). The interference with QS can in general be achieved by inhibition of signaling molecule synthesis, inhibition of signal transport, inhibition of molecule–receptor interaction, modification or degradation of signaling molecules or by antagonistic small molecules (Grandclément et al., 2016; Weiland-Bräuer and Schmitz, 2017). However, recent evidence shows that QS is not restricted to the domain of bacteria, but also allows communication between bacteria and their hosts. The research field of “interkingdom signaling” is still in its infancy, but the increasing number of publications in this area demonstrates that microbe–host communication is in the spotlight. Prominent examples of microbe–host communication, which illustrate the enormous impact of bacteria–host interactions on the development and evolution of a metaorganism, will be presented in the following.

The first example of interkingdom signaling between bacteria and plants was found in the relationship between the marine bacterium *Vibrio anguillarum* and the green seaweed *Enteromorpha* (Joint et al., 2002). Biofilm-forming *Vibrio* cells release N-acyl homoserine lactones (AHLs) and attract zoospores, the motile reproductive stage of the seaweed, which subsequently settle to establish and develop in a certain habitat. The specific response of a plant to bacterial AHLs was first shown for the legumes *Phaseolus vulgaris* (Joseph and Phillips, 2003) and *Medicago truncatula* (Mathesius et al., 2003). Here, AHLs from both symbiotic (*Sinorhizobium meliloti*) and pathogenic (*Pseudomonas aeruginosa*) bacteria caused significant changes in the gene expression of the plants. The probably most-studied plant–bacteria interaction occurs in the red alga *Delisea pulchra,* which secretes brominated furanones to protect itself from fouling microorganisms. The algae release brominated furanones which inhibit multiple AHL-dependent processes including swarming motility in *Serratia liquefaciens* and bioluminescence in *Vibrio* species as well as AI-2-based QS in *Vibrio* species (Givskov et al., 1996; Nys et al., 2006). However, one of the best-studied interkingdom signaling mechanisms is found in the relationship between *Rhizobium* spp. and their symbiotic legume host. In this symbiosis, a complex exchange of signals between bacteria and plant leads to the successful formation of root nodules in which bacteria reside and fix atmospheric nitrogen (Sanchez-Contreras et al., 2007). In summary, plants have evolved multiple mechanisms to interpret bacterial QS signals and initiate attraction/defense responses in a tissue-specific manner, which are even signal-specific (Mathesius et al., 2003; Bauer and Mathesius, 2004).

During the last decades, scientists have realized that bacterial signals are also able to modulate signal transduction and immune responses of animal hosts (Telford et al., 1998; Kravchenko et al., 2008), and, conversely, that host hormones can modulate bacterial gene expression (Sperandio et al., 2003). The AI-3/epinephrine/norepinephrine signaling system is the prime example. The enteric pathogen *Escherichia coli* uses AI-3 produced by the microbial gastrointestinal (GI) community to activate the expression of its virulence genes, resulting in colon lesions. In enterohemorrhagic *E. coli* (EHEC), the eukaryotic hormones epinephrine and norepinephrine present in the GI tract also activate the expression of its virulence genes (Sperandio et al., 2003). Thus, EHEC “captures” the eukaryotic hormones to promote its colonization of the human colon mucosa causing colon lesions. Opioids such as endorphin and dynorphin are also known to be hijacked by pathogenic bacteria like *P. aeruginosa*. The bacteria recognize and use those opioids to enhance their virulence by increasing the production of their three QS systems, leading to persistent *P. aeruginosa* colonization in the lungs of cystic fibrosis patients (Zaborina et al., 2007). In addition, it was recently shown that mammalian epithelial cell cultures produce an AI-2 mimic that activates QS-controlled gene expression, e.g. in the enteric pathogen *Salmonella typhimurium* (Ismail et al., 2016). Further studies have found cytoplasmic factors in mammalian cells that degrade 3-oxo-C12-HSL, most likely to prevent interference with host cellular functions. Those paraoxonases (PONs) are involved in the detoxification of many organophosphates and additionally act as lactonases, cleaving the lactone ring of AHLs to make them ineffective (Kiran et al., 2017).

Interkingdom communication also occurs in early-branching metazoans. In the freshwater cnidarian *Hydra* a new eukaryotic QQ mechanism was identified, which enables the polyp to specifically modify long-chain 3-oxo-HSLs by oxidoreductase activity (Pietschke et al., 2017). In addition, whole-genome sequencing of *Hydra*'s main bacterial colonizer *Curvibacter* sp. revealed the presence of LuxI/LuxR homologs. Functional characterization of the QS systems of *Curvibacter* sp. showed that both the host-modified and the non-modified AHL version were recognized by the same AHL receptor. Remarkably, even though both AHLs were recognized by the same receptor, gene expression profiles of the bacterium differed depending on the AHL version present. Investigating the impacts of the different QS signals on metaorganism assemblies in vivo elucidated that the host-modified signal promotes, while the non-modified signal represses, symbiont colonization. These results suggest that *Hydra* is able to regulate the behavior of its bacterial colonizer to promote metaorganism assembly and resilience (Pietschke et al., 2017).

To identify QQ activities of *Aurelia aurita*-associated microbes, over hundred bacteria were isolated from different life stages of the jellyfish, of which 25% showed QQ activities against AHL as well as AI-2-mediated QS using a recently established reporter system (Weiland-Bräuer et al., 2015, and unpublished data). Selected isolates have been further characterized to identify the QQ-conferring open reading frames (ORFs) (Weiland-Bräuer et al., 2015, and unpublished data); first, to gain insight into the bacteria–bacteria communication and its impact on host colonization; and second, to unravel possible protective effects for the host. In addition, several QQ-ORFs of the host, whose gene expression patterns are currently under investigation, were identified (Weiland-Bräuer et al., unpublished data).

Those examples clearly show that QS and QQ are common languages used in many metaorganisms. Thus, QS and QQ may represent a general language of communication that spans different domains of life and has evolved early during the co-evolution of bacteria and eukaryotic hosts. Future studies in this field will enhance our understanding of the signaling networks that have driven the co-evolution of prokaryotes and eukaryotes.

5. Living in the soil: rhizosphere microbes and plant stress tolerance

Soil-grown plants are immersed in a multitude of microbes and diverse beneficial microorganisms such as plant growth-promoting bacteria (PGPB) as well as plant growth-promoting fungi (PGPF). The root-associated microorganisms, generally denoted as the rhizosphere, receive a considerable fraction of photosynthetic products from their host plants. However, plants require significant quantities of nitrate, phosphate and other minerals from the soil to support their growth and development. These soil components are often only available in limited quantities or in inaccessible forms, but can be made available through rhizosphere microbes. While mycorrhizae provide phosphate and nitrate to plants, free-living or endophytic rhizobia can fix atmospheric nitrogen (Corradi and Bonfante, 2012; Geurts et al., 2012). Other beneficial microbes can confer enhanced resistance to biotic and abiotic stresses (Lugtenberg and Kamilova, 2009). The establishment of beneficial plant–microbe interactions requires the mutual recognition and a considerable orchestration of the responses at both the plant and the microbial side and in this way contributes to the establishment of the complex microbial communities that are shaped by soil- and plant-specific features. The interaction mechanisms are best understood in

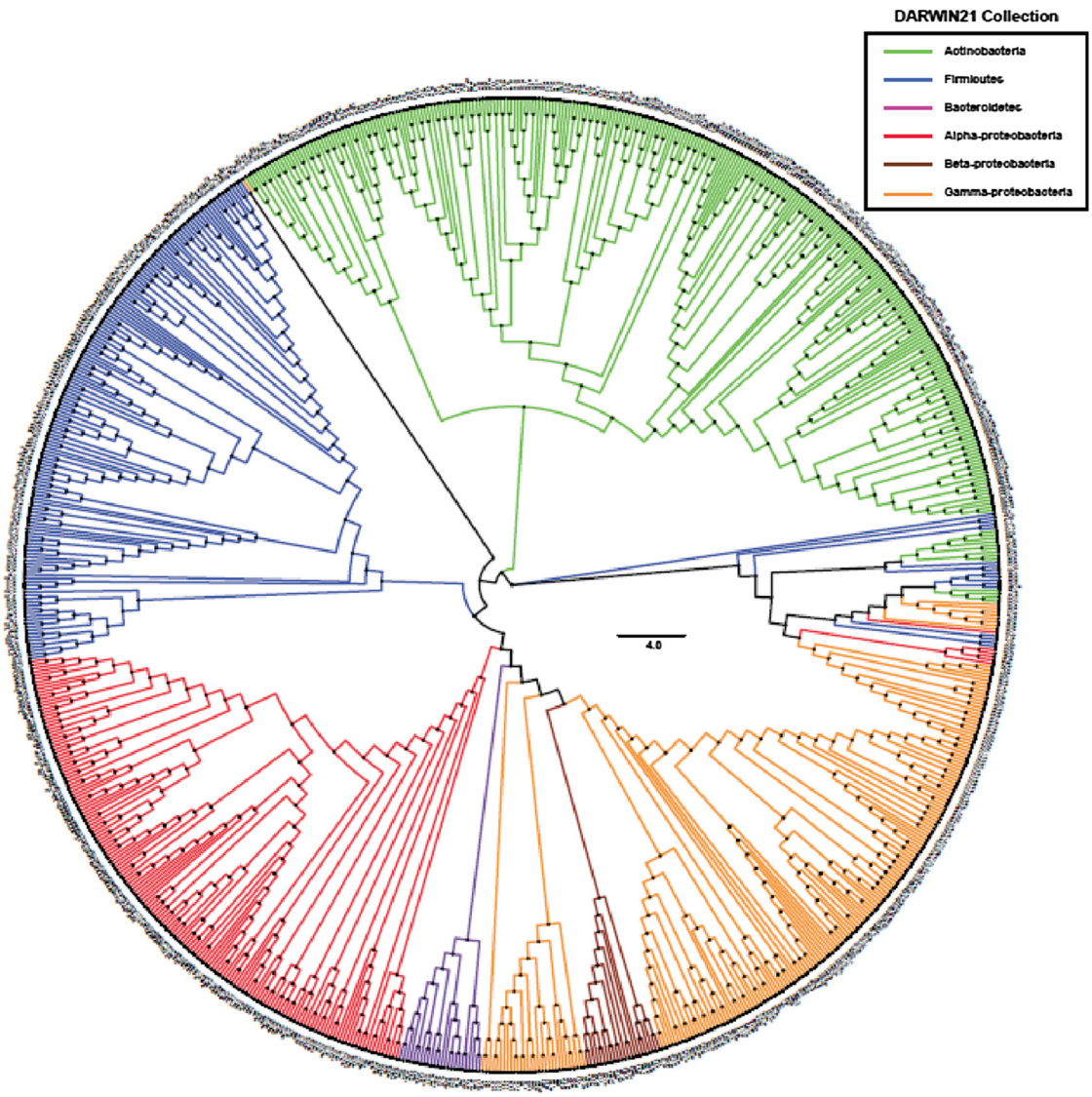

Fig. 4. Phylogenetic tree of the DARWIN21 bacterial collection based on 16S rRNA gene sequence comparison. Evolutionary relationships of bacterial isolates obtained by multiple alignment of the nucleotide sequences by MUSCLE (Edgar, 2004). The phylogenetic tree was constructed by the neighbor-joining method, based on the Kimura 2-parameter model, with bootstrap analysis (1000 replications) using the software MEGA (version 7; Kumar et al., 2016).

rhizobial and mycorrhizal symbioses which share a common plant signaling pathway that is activated by the distinct factors that are produced by each microbe (Corradi and Bonfante, 2012). The same signaling pathway also seems to be activated by certain beneficial bacteria, suggesting that different beneficial and pathogenic microbes initiate common plant signaling pathways. Evidence also indicates that beneficial and pathogenic microbes suppress the host defense system by a number of different strategies, including the production of effectors, exopolysaccharides, or phytohormones (Zamioudis and Pieterse, 2012).

Different bacterial families can improve the growth of vegetables and crops under abiotic stress conditions (Egamberdieva and Kucharova, 2009). Enhanced salt tolerance of *Zea mays* upon co-inoculation with *Rhizobium* and *Pseudomonas* is correlated with decreased electrolyte leakage and maintenance of leaf water contents (Bano and Fatima, 2009). Some microorganisms produce plant hormones, such as indole acetic acid and gibberellic acid, which induce increased root growth and thereby lead to enhanced uptake of nutrients (Egamberdieva and Kucharova, 2009). PGPBs can also induce systemic resistance to pathogens and prime the plant innate immune system to confer resistance to a broad spectrum of pathogens with a minimal impact on yield and growth (Van Hulten et al., 2006). A variety of PGPBs colonizes roots and has been shown to protect a large variety of plant species, including vegetables, crops, and even trees, against foliar diseases in greenhouse and field trials (Van Loon, 2007).

PGPF, such as mycorrhizal and endophytic fungi, can also interact with many plant species and thereby significantly enhance stress tolerance of the plants against a variety of conditions, including drought, heat, pathogens, herbivores, or limiting nutrients (Rodriguez et al., 2008). Interestingly, some plants are unable to withstand stress conditions in the absence of their associated microbes, as, for example, shown for the geothermal plant *Dichanthelium lanuginosum* which interacts with the fungus *Curvularia protuberata*. While *C. protuberata* confers heat tolerance to *D. lanuginosum* plants, neither the fungus nor its host plant can survive alone at elevated temperatures (Redman et al., 2002). Some PGPF can also have a dual nature, being beneficiary to their host plants, but pathogenic to non-host plants, as shown, for example, for *Colletotrichum acutatum*, which is a pathogenic ascomycete for strawberry, but beneficial when colonizing pepper, eggplant, bean, and tomato (Freeman et al., 2001). Depending on the PGPF, biotic stress tolerance appears to be conferred by different mechanisms. For example, a non-pathogenic *Colletotrichum* confers disease resistance but does not activate defense in the host plant in the absence of a pathogen

infection. Moreover, the defense response is confined to fungus-colonized tissues (Redman et al., 1999). In contrast, the fungus *Piriformospora indica* (Sebacinales) colonizes the roots of many plant species and confers disease resistance systemically (Stein et al., 2008).

Microbes seem to be able to ameliorate plant stress responses to abiotic environmental stresses by influencing not only physiological but also developmental processes of plants (De Zelicourt et al., 2013). This is best exemplified by the modification of the root systems of the host plants by various beneficial microbes (Egamberdieva and Kucharova, 2009). In contrast to plants, which have relatively stable genomes and long life cycles, microbes have short generation times and can evolve a high degree of genetic diversity on short time scales. These attributes allow for rapid changes in microbes and for the development of new compounds that can influence the biochemical regulation of key steps of the plant system. This enormous capacity for generating novel compounds from scratch has been seen in the incredible inventory of pathogen effectors (Toruño et al., 2016), and it cannot be excluded that beneficial microbes have also developed a battery of factors which help plants to rapidly respond to environmental changes to which the plant genomes are only slowly adapting.

6. Adaptation of plant metaorganisms to desert conditions

Ever since the colonization of land, plants have evolved mechanisms to settle and survive even in extreme habitats, such as deserts. In spite of the challenging conditions of desiccation and low nutrient availability, desert plants can also support a diversity of rhizosphere microorganisms. These observations pose the question how the growth of desert plants is possible under extreme conditions when most other plants from temperate zones quit long before. Besides specific morphological and physiological adaptations that are fixed in the plant genetic system, the discovery of specific microbial strains conveying heat, drought or salt tolerance suggests alternative explanations (De Zelicourt et al., 2013).

In particular, the ability of the desert PGPF *P. indica* to stimulate the growth of many plants and crops by promoting nitrate and phosphate uptake and at the same time conferring resistance against abiotic and biotic stresses (Waller et al., 2005; Stein et al., 2008) laid the ground for launching the DARWIN21 project with the aim to systematically search for beneficial rhizosphere microbes in different deserts and use them to develop an organic and sustainable agriculture. So far, the DARWIN21 project (http://www.darwin21.net/index.htm) has generated over 1500 culturable microbial strains from various deserts in the Middle East (Fig. 4). These strains are tested on a plant stress phenotyping platform for their capacity to confer salt, drought and heat tolerance on both model and crop plants, and selected elite strains are used for their performance with local crops in field trials. For certain beneficial microbes, transcriptome, proteome and metabolome analyses of both the microbes and the host plants have been conducted to better understand the communication, signaling and metabolic processes between the symbiotic partners. A genetic model system was established for the symbiotic interaction of several highly divergent bacterial genera with the genetic model plant *Arabidopsis thaliana*, and both reverse and forward genetic screens have been launched for both host plant and microbial partner. The search for new medicinally important chemical compounds complements the metabolic network reconstruction from the fully sequenced microbial genomes and also opens the door for large-scale comparative genomics. Together with the above approaches, DARWIN21 is expected not only to help establish a future sustainable agricultural system, but also to develop new applications in medicine, chemical engineering and synthetic biology.

7. Invertebrates in the intertidal zone

The intertidal zone is a marine habitat that is characterized by periodical changes between high and low tide. The daily fluctuations in water level shape microhabitats with rapidly changing and extreme conditions with regard to light intensity, UV radiation, temperature, oxygen, and salinity. These environmental extremes exert high stress on intertidal organisms. For example, temperature oscillations of up to 20 °C daily (Fraune et al., 2016), salinities of up to 51‰ (Hand and Uhlinger, 1995), and direct air and sun exposure pose challenges to organisms living in this habitat. Therefore, predominately sessile species must have considerable physiological plasticity, i.e., a strong ability to acclimatize, paired with genetic adaptations to thrive in the intertidal zone. For instance, polychaetes and other organisms that live in high marsh estuarine environments (i.e., the upper intertidal zone) are typically characterized by reduced genetic connectivity between populations and local adaptations (Bilton et al., 2002; Virgilio et al., 2006). Thus, animals that colonize the intertidal zone are interesting study objects to probe for adaptation mechanisms to extreme environments. Currently, two animal groups of the Anthozoa, namely sea anemones with their representative *Nematostella vectensis* and stony corals are used to investigate the mechansisms of adaption to these highly variable environments.

Nematostella vectensis occurs in brackish habitats, particularly in tide pools of the high marsh along the Atlantic coast of the United States and Canada (Hand and Uhlinger, 1994; Reitzel et al., 2008). In its north–south distrubition *Nematostella* spans a thermocline of around 10 °C mean temperature over 10° latitude (Hand and Uhlinger, 1994; Reitzel et al., 2008), which has resulted in different thermal optima for growth and thermal tolerance in different populations (Reitzel et al., 2013a). These differences in optimal growth conditions and stress resistance are correlated with genetic differentiation between populations (Pearson et al., 2002; Darling et al., 2004; Reitzel et al., 2008). Comparisons of allele frequencies support the hypothesis that some of this genetic variation is a result of natural selection (Sullivan et al., 2009; Reitzel et al., 2013b). Although there is significant genetic and phenotypic variation between populations of *Nematostella*, individuals from different populations are interfertile (Hand and Uhlinger, 1994; Reitzel et al., 2008), allowing the generation of hybrid lines and their further investigation in the laboratory.

Tropical and subtropical coral reefs extend from deep in the subtidal zone, where corals experience relatively stable environmental conditions, to the shallow intertidal zone, where they have developed mechanisms to cope with large environmental fluctuations. As illustrated by examples from American Samoa (Oliver and Palumbi, 2011), Florida (Kenkel et al., 2013), and Western Australia (Schoepf et al., 2015), corals from these highly variable environments are generally more heat tolerant. This increased heat tolerance is at least in part explained by (long-term) adaptation and (short-term) acclimatization processes in the coral host (Palumbi et al., 2014). Corals from highly variable environments are characterized by genomic adaptations (as detected by RNA-based single nucleotide polymorphisms) that may give them an advantage over their less exposed conspecifics under extreme environmental fluctuations (Bay and Palumbi, 2014; Palumbi et al., 2014). The higher acclimatization capacity of corals from highly variable environments may further be related to 'front-loading' of stress tolerance genes (Barshis et al., 2013) and a parallel muted transcriptional stress response (Bay and Palumbi, 2015). Generally, their capacity for acclimatization is determined by the high variability of the environment, which promotes more flexible corals with higher acclimatization capacity (Kenkel and Matz, 2016).

Bacteria and other microbial organisms are also a vital component of cnidarian holobionts (Rohwer et al., 2002; Fiore et al., 2010; Fraune et al., 2014; Torda et al., 2017). The anemone *Nematostella* is characterized by a stably associated bacterial community, which is highly dynamic but conserved in response to host development (Mortzfeld et al., 2016). Long-term acclimation to different environmental conditions results in reproducible shifts in the associated bacterial community, e.g. in an increase of rare bacterial species (Mortzfeld et al., 2016). In addition, polyps of natural populations of *Nematostella* reveal a

strong correlation between host biogeography and bacterial diversity (Mortzfeld et al., 2016), which may represent a mechanism to buffer the impact of the environment on the holobiont (Rosenberg et al., 2007).

In shallow-growing corals, subaerial exposure during summer or noon low tides can lead to coral bleaching, which is the loss of the obligate endosymbiotic dinoflagellates (*Symbiodinium* spp.) from the coral host tissue (Brown et al., 1994). However, coral hosts in the intertidal zone can be associated with particularly tolerant *Symbiodinium* species (Oliver and Palumbi, 2010). But, in contrast to the coral host, *Symbiodinium* shows no transcriptional heat stress response (Barshis et al., 2014). Instead, post-transcriptional RNA editing has recently been implicated as an alternative mechanism of acclimatization in these coral endosymbionts (Liew et al., 2017). Much less is known about how environmental variability influences other coral-associated microbes, such as bacteria, and how environmental variability influences the interplay between the host and these microbes. Generally, coral-associated bacterial communities on reef flats can quickly change with tidal cycles, with younger colonies exhibiting changes faster than older colonies (possibly due to a more stable microbiome) (Sweet et al., 2017). Further, bacterial communities in highly variable reef flat environments are distinct from those in less extreme conditions, and bacterial community dynamics are linked to the heat tolerance of their coral host (Ziegler et al., 2017).

Fast changes in bacterial communities may thus represent a mechanism for cnidarian holobionts to adjust to rapidly changing environmental conditions in the tidal zone and possibly to environmental changes elsewhere (Ziegler et al., 2017). Potential microbial mechanisms to facilitate holobiont acclimatization include processes such as symbiont shuffling (proportional changes of microbiome members) and switching (loss or acquisition of microbes), mutations in bacterial genomes, and horizontal gene transfer (Buddemeier and Fautin, 1993; Reshef et al., 2006; McFall-Ngai et al., 2013; Fraune et al., 2016; Theis et al., 2016; Webster and Reusch, 2017). The level of flexibility in regard to metaorganism structure and associated acclimatization potential, however, may drastically differ between holobiont assemblages. Red Sea *Pocillopora verrucosa* corals, for instance, maintain structurally stable symbiotic algal assemblages and bacterial microbiomes even under adverse environmental conditions (Ziegler et al., 2015; Ziegler et al., 2016; Pogoreutz et al., 2018). In light of Ziegler et al. (2017) suggesting that coral microbiome adaptation aligns with increased stress resistance, the contrasting high stress susceptibility of the stable *P. verrucosa* holobiont may provide evidence that coral holobionts in fact harbor differing levels of microbiome flexibility with consequences for their ability to respond to environmental disturbance (Pogoreutz et al., 2018). Yet, it remains to be determined whether microbiome flexibility is the cause or consequence of physiological instability in a stressed holobiont (Grottoli et al., 2018). More research is needed to understand the potential roles and the contribution of bacterial communities to holobiont acclimatization and adaptation on short time scales (Torda et al., 2017). In particular, knowledge on acclimatization and adaptation mechanisms of organisms inhabiting extreme environments such as the intertidal zone may give insights into organismal responses to scenarios of a changing climate on a global scale.

8. Coral reefs in the oligotrophic seas

The tropical open ocean is characterized by warm, sunlit, and nutrient-poor (oligotrophic) waters, the latter factor ultimately limiting its primary productivity (Vitousek and Howarth, 1991). Nonetheless, highly productive shallow-water ecosystems such as coral reefs or seagrass beds flourish along its coastlines even in the absence of major nutrient input (Connell, 1978; Hatcher, 1990). The apparent contradiction of high ecosystem productivity in nutrient-poor tropical waters was first observed by Charles Darwin, and was hence coined the 'Darwin Paradox' (Darwin, 1842; Sammarco et al., 1999). Today we know that the high productivity of these ecosystems is enabled by functional traits of their key ecosystem engineer species, such as sponges, seagrasses, or reef-building (scleractinian) corals (Muscatine and Porter, 1977; Wild et al., 2004b; De Goeij et al., 2013). These engineers constitute complex metaorganisms (holobionts) comprising an animal or plant host living in intimate association with a diverse suite of prokaryotic and eukaryotic partners (Wilkinson and Fay, 1979; Rohwer et al., 2002; Thomas et al., 2016).

The critical importance of these holobionts for ecosystem health and functioning is best illustrated by the scale of coral reef ecosystems. Coral reefs can attain physical structures of hundreds to more than 2,000 kilometers in size, such as the Great Barrier Reef (Birkeland, 1997). The structural and functional basis of this ecological success is mainly provided by scleractinian corals, due to their calcium carbonate skeletons that build the structural backbone of reef ecosystems. Cnidarians are highly adapted to life in the tropical oligotrophic ocean and significantly contribute to the high primary production on reefs (Muscatine and Porter, 1977; Falkowski et al., 1984; Yellowlees et al., 2008). Primary production in the coral holobiont is mainly attributed to the coral–algal endosymbiosis, a mutualistic nutrient exchange relationship between the coral animal host and the algal endosymbiont *Symbiodinium* (Muscatine and Porter, 1977; Falkowski et al., 1984, 1993; Muscatine and Kaplan, 1994). In this intimate symbiosis, a heterotrophic multicellular organism is hosting a photoautotrophic partner, a rare holobiont constellation known from only few other host–microbe systems, such as between *Symbiodinium* and other Cnidaria, giant clams (genus *Tridacna*), nudibranchs (Ziegler et al., 2014), and Foraminifera (Mies et al., 2017), or the *Hydra viridis–Chlorella* association (Muscatine et al., 1975; Muscatine and Neckelmann, 1981; Bosch, 2012; Habetha et al., 2003).

The unique constellation of the coral holobiont facilitates reef nutrient (re)cycling on all levels of biological organization: on the cellular level, nutrient cycling and recycling is mainly driven by the coral–algae symbiosis (Hatcher, 1990; Muscatine and Kaplan, 1994; Yellowlees et al., 2008; Rädecker et al., 2017). Here, the coral provides inorganic nitrogen compounds (along with other compounds such as carbon dioxide) from its catabolism to the algal symbionts, thereby tightly regulating their population density and growth (Muscatine and Porter, 1977; Rahav et al., 1989; Falkowski et al., 1993). Presumably elicited by a group of free amino acids provided by the coral, so-called host release factors, *Symbiodinium* in turn translocates most of its photosynthates (organic carbon, i.e., sugars and amino acids) to the coral host (Gates et al., 1995). On the holobiont level, bacteria (and other microbes) further contribute to nutrient cycling, helping maintain productivity (Lesser et al., 2007; Wegley et al., 2007; Raina et al., 2010; Cardini et al., 2015; Rädecker et al., 2015; Benavides et al., 2016). As a result of this productivity, the coral holobiont can afford the release of more than 50% of its organic carbon (i.e., mucus) into the water column (Wild et al., 2004b). Here, the coral-derived organic carbon enters the reef food web via the microbial and sponge loop (Wild et al., 2004b, 2004b; De Goeij et al., 2013; Rix et al., 2016). Briefly, the released coral mucus traps suspended particles and is subsequently mineralized in the coral reef sediments (Wild et al., 2004a,b) or via the sponge loop (De Goeij et al., 2013; Rix et al., 2016), thereby reducing the loss of energy and nutrients from the reef. Coral (and sponge) holobionts thereby widely contribute to the recycling of nutrients via the (re)generation and transformation of (in)organic matter even on the ecosystem scale (Wild et al., 2004a; De Goeij et al., 2013; Cárdenas et al., 2015; Cardini et al., 2015, 2016; Rix et al., 2016). Curiously, much of the energy released by scleractinian corals is rapidly channelled into higher trophic levels on pristine reefs, resulting in inverted, top-heavy biomass pyramids, i.e., high biomasses of apex predators and low biomasses of primary producers (DeMartini et al., 2008; Rohwer et al., 2010), which is unparalleled by any other ecosystem on Earth. Thereby, the high productivity of coral reefs extends well beyond its ecosystem boundaries even into the human realm, sustaining the livelihoods of some 500

billion people via the provisioning of food (reef fisheries), coastal protection, and income from tourism (Moberg and Folke, 1999).

The peculiar constellation of the coral holobiont not only allows for an efficient cycling of nutrients, but may also convey disease and stress resistance and drive adaptation via the rapid restructuring of microbial communities (Reshef et al., 2006; Rosenberg et al., 2007; Krediet et al., 2013; Torda et al., 2017; Ziegler et al., 2017). Consequently, microbial dysbiosis, i.e. the disruption of the coral–algae symbiosis (bleaching) or the coral bacterial community, can lead to holobiont breakdown (Pogoreutz et al., 2017a, 2018), its potentially devastating effects rapidly cascading on to the ecosystem level, ultimately resulting in the local or regional extirpation of coral reefs (Hughes et al., 2003, 2017).

Scleractinian corals are complex and diverse metaorganisms shaping highly productive coral reef ecosystems in the oligotrophic tropical ocean. Thereby, corals and the reefs they shape share common drivers from the cellular to the ecosystem level, rendering the coral holobiont a micro-ecosystem – and the coral reef a holobiont of impressive spatial scales. Similarly, the implications of disrupted holobiont functioning, in particular bleaching, extend well beyond the individual colony level, threatening marine ecosystems on a global scale (Hughes et al., 2017, 2018). Disentangling the complex interactions within the coral as well as the 'ecosystem holobiont' will therefore be critical to our understanding of their stress responses from the micro- to the macro-scale (Voolstra et al., 2015; Putnam et al., 2017).

By comparison, the symbioses between marine sponges (phylum Porifera) and associated microbial consortia are much less understood. Sponges harbor dense and diverse microbial communities extracellularly within the sponge matrix and are thus excellent examples of marine holobionts (Hentschel et al., 2012; Webster and Thomas, 2016). Sponges influence ecosystem functioning by modifying biotic and abiotic factors (Bell, 2008). For example, they provide habitat for a wide range of fauna and play an important role in benthic–pelagic coupling due to their impressive filtering capacity (De Goeij et al., 2013; Rix et al., 2016). Novel meta-omic approaches have begun to reveal the functions of the collective microbial community and individual symbiont groups (Thomas et al., 2010; Jahn et al., 2016; Lackner et al., 2017; Moitinho-Silva et al., 2017a; Slaby et al., 2017). One major finding is that many of the functional roles provided by sponges are indeed mediated by their associated microbes. Another finding is that sponges can generally be classified into two groups according to the abundance and density of microbes in their tissues. High microbial abundance (HMA) sponges harbor densities of microbes 2–4 orders of magnitude higher than low-microbial abundance (LMA) sponges (Moitinho-Silva et al., 2017b). Therefore, the experimental combination of HMA and LMA sponges can reveal the role and function of sponge microbes in the process under investigation. This natural variability across sponge holobionts and environments, together with the possibility of laboratory experiments, opens up the opportunity to address the dynamics of these complex symbiotic systems under climate change scenarios (Pita et al., 2016).

9. Hydrothermal vents

Since their discovery in 1977 during the exploration of the Galapagos Spreading Center, hydrothermal vents have been considered one of the most productive primary biomass producer habitats on Earth. These areas are typically located at depths greater than 1000 m, below the euphotic zone, and can be characterized by submarine springs that emanate from the sea floor and contain high concentrations of reduced energy sources – mainly hydrogen sulfide and methane. These nutrient-rich flows allow the establishment of successful invertebrate communities worldwide based on symbiosis interactions with microbial chemoautotrophic producers (Van Dover, 2000).

The invertebrate species found in hydrothermal vents belong to the phyla Mollusca, Annelida or Arthropoda. Mollusca is the most diverse group, with one worm species from the class Aplacophora, several clam and mussel species from the class Bivalvia and some snail and limpet species found within the Gastropoda group. As for the Annelida phylum, up to four worm species of Polychaeta could be described so far. This community also comprises one shrimp and one crab species from the Decapoda subgroup (Dubilier et al., 2008). One of the best-known examples of these associations is perhaps the symbiosis between the gutless giant tube worm of the genus *Riftia* and its sulfur-oxidizing bacteria (Cavanaugh et al., 1981). *Riftia* larvae are free-swimming organisms. When they reach the juvenile stage, they become sessile and acquire the bacteria from fresh water through the skin. After the infection, sharp developmental changes occur, giving rise to the development of the specialized trophosome tissue which harbors the symbionts (Nussbaumer et al., 2006). The larvae use their characteristic and highly vascularized red plume to exchange compounds with the water and thus provide the endosymbionts with nutrients (Minic and Hervé, 2004). *Bathymodiolus* mussels and *Calyptogena* clams are also capable of establishing associations with intracellular chemosynthetic bacteria that inhabit the bivalve gill epithelium. While so far only sulfur-oxidizing bacteria have been discovered in clams, some *Bathymodiolus* species, such as *B. azoricus* and *B. broksii* from the Gulf of Mexico, also harbor methanotrophic symbionts (Kuwahara et al., 2007; Ponnudurai et al., 2017). Another characteristic that differentiates both bivalves is the transmission mode. While it has been shown that in clams the bacteria are acquired vertically, in mussels this occurs horizontally and most likely by means of a continuous process during the whole lifetime of the host (Wentrup et al., 2014). *Alviniconcha* is one of the few examples of marine invertebrates that harbors thioautotrophic symbionts related to Epsilonproteobacteria inside their gills. These deep-sea snails are also believed to take up the endosymbionts from the environment (Suzuki et al., 2005).

Chemoautotrophy is the basis of all these symbiotic interactions. In this special type of metabolism, the energy required for the fixation of the inorganic carbon is obtained by oxidizing the reduced compounds that emanate from the hydrothermal vents. In this way, bacteria become the primary producers to support this biological community. The main two symbiont functional groups are thiotrophic and methanotrophic bacteria belonging to the Gammaproteobacteria clade, although in a few cases the thiotrophs could be identified as Epsilonproteobacteria (Nakagawa and Takai, 2008). Phylogenetic analyses revealed that sulfur-oxidizing endosymbiont clades are usually interspersed with other free-living Gammaproteobacteria, indicating that the establishment of these symbiont associations has evolved several times in a convergent manner (Petersen et al., 2012). In addition, different transmission modes may explain the acquisition of the symbionts by the host. While some species show vertical transmission from the parental host to the offspring, in many cases the symbionts are directly acquired from the sea water. Recent studies revealed a mixed transmission of the symbionts in the shallow-water *Solemya velum* symbiosis, suggesting that this genetic diversity may be related to the adaptation of the hosts to environmental changes (Russell et al., 2017). Also, the morphological plasticity of these interactions can vary among different host, from epibionts attached to the mouth appendages and gill chambers of vent shrimps to endobionts that can be associated either extracellularly – as in the case of gutless oligochaetes – or intracellularly as in most of the bivalves.

In conclusion, hydrothermal vents may be perceived as the oases of the deep sea. In this hostile environment, factors such as the absence of light and low oxygen concentration prevent the settlement of animal communities in the vast majority of areas. It is only the establishment of symbiotic associations with microbes that has permitted the development of animal diversity in the deep sea.

10. The forgotten players: viruses and archaea

In the last decade research has focused on the elucidation of host-associated bacterial communities. The development of new sequencing

technologies, the availability of universal primers targeting bacterial communities and well established analysis pipelines facilitated the entry of many researchers from different disciplines into the field of host–bacterial interaction. During the last years, intensive microbiome research has uncovered the essential role(s) microorganisms play in regard to the physiology of their hosts (McFall-Ngai et al., 2013). While the use of eubacterial 16S rRNA gene primers targeting the V1–V2 or V3–V4 regions is well established in most research facilities, the use of different primer sets targeting other host-associated microorganisms, such as archaea, viruses, protozoans or fungi is still in its infancy. Thus, the majority of these studies has overlooked these microbiome members, most probably due to methodological challenges and underestimated significance.

10.1. Viruses

Viruses are the most abundant entity in the world (Suttle, 2005) and are known to be important regulators within ecosystems (Brussaard, 2004; Suttle, 2016). This regulatory role of viruses can also be expected within metaorganisms. However, viruses as associated partners of metaorganisms cannot be compared to bacteria without prior exploration. The main reasons why viruses have been almost completely neglected are their high diversity and the fact that they are composed of dsDNA, ssDNA, dsRNA, ssRNA or a mixture of both DNA and RNA. In addition, viruses feature high mutation rates and thus are lacking any conserved genes that can be targeted by PCR (Sanjuán et al., 2010). Nevertheless, recent studies exploited large-scale sequencing datasets to identify viral sequences that were present as a sort of by-catch (Brüwer and Voolstra, 2017; Brüwer et al., 2017). Although such an approach comes with its own set of limitations and caveats, it provides a first insight into viral diversity and how it aligns with environmental or species differences.

Yet, to get an in-depth understanding of viral communities within metaorganisms, one cannot simply isolate DNA or RNA from host tissue, biopsies, surface swabs or fecal samples. Viral particles have to be isolated and separated from host tissue and purified from contaminating nucleic acid (Fig. 5). The separation of viruses from host tissue is not trivial as many host compounds can bind viral particles leading to aggregates (Ueda et al., 2013; Gerba and Betancourt, 2017) which may get lost during subsequent purification processes like filtration or low-speed centrifugation. The choice of the correct extraction buffer and the use of subsequent purification steps such as gradient density ultracentrifugation and digestion of contaminating host DNA and RNA by nucleases are labor intensive and prone to experimental biases. Giant viruses such as Mimiviridae and Pandoraviridae might get lost by filtration. Some virons are sensitive towards nuclease digestion at higher pH values, while some are unstable in extraction buffer, chloroform or cesium chloride (Wetz and Kucinski, 1991; Hema et al., 2010).

Another important point is that not all host-associated viruses are present in their encapsulated form, where viral nucleic acid is protected from enzymatic digestion by viral capsid proteins. During latent viral infections of eukaryotic hosts but also during the lysogenic state of temperate phages, viral sequences are integrated into the genome of their host or are present in the form of an episome in the cell. Most of these viruses are transcriptionally active and interact with the metaorganism. These viruses can only be identified by metagenomics and metatranscriptomics (Bikel et al., 2015). However, missing reference data or viral sequence data partially wrongly annotated as part of the host genome make it difficult to identify these viruses. Especially when working with non-model organisms with limited information about the host genome it is difficult to distinguish viral sequences. Finally, it has to be pointed out that the viral community of metaorganisms originates from the eukaryotic host and its associated eukaryotic and prokaryotic partners. In order to understand the function of viruses within metaorganisms the viral community has to be linked back to their specific interacting partners (viral host for replication) within the metaorganism.

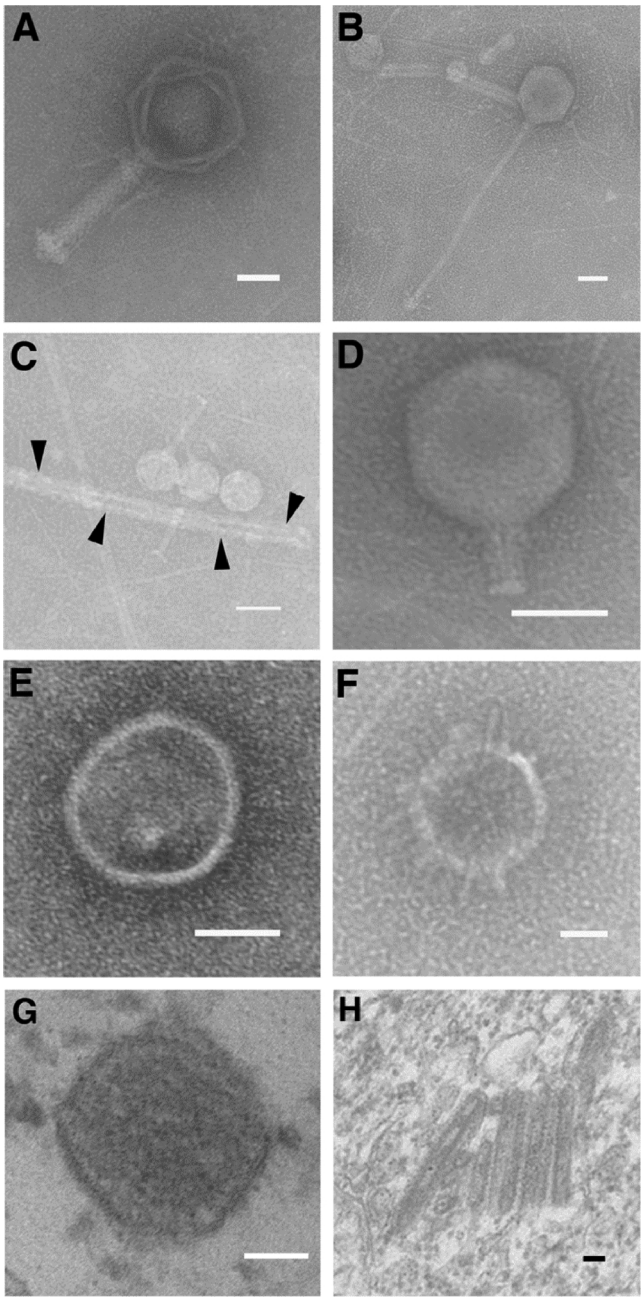

Fig. 5. Species-specific viromes in the ancestral holobiont *Hydra*. Transmission electron micrographs of negatively stained viruses from the freshwater polyp *Hydra*. Many viral families have been identified, including bacteriophages: (A) Myoviridae, (B) Siphoviridae, (C) Inoviridae (arrows point towards Inoviridae virion), (D) Podoviridae; as well as eukaryotic viral families: (E) Herpesviridae, (F) Phycodnaviridae, (G) tissue-bound Herpesviridae, and (H) Baculoviridae. Scale bars = 50 nm (Grasis et al., 2014).

10.2. Archaea

Since 1977, archaea have been described as unique prokaryotic organisms that are neither bacteria nor eukaryotes (Woese and Fox, 1977). Carl Woese and colleagues (Woese and Fox, 1977; Woese, 1987; Woese et al., 1990) found explicit differences between the sequence identities of the 16S rRNA gene sequences and the RNA polymerases of archaea, bacteria and eukaryotes and thus proposed that Archaea form an evolutionarily independent domain. In the following years, more individual properties of archaea were observed. These include their

unique chemical cell membrane composition that is composed of L-glycerol-ether lipids whose sidechains consist of isoprenoids (De Rosa et al., 1986; Koga et al., 1993; Koga and Morii, 2005, 2007). Moreover, the cell wall of archaea is highly diverse and includes not only surface layer proteins, but also pseudomurein as well as methanochondroitin (Kandler and König, 1998). In contrast to their overall morphological similarity to bacteria, archaea share several cellular characteristics with their eukaryotic counterparts, e.g. regarding their translation and transcription machinery (Cavicchioli, 2007). Recent studies even hypothesize that eukaryotic hosts evolved from an archaeal ancestor in which numerous components with eukaryote-specific features are found (Spang et al., 2015; Adam et al., 2017).

In the meantime, the diversity found within the domain Archaea has become incessantly higher and their phylogeny has been continuously updated – with the biggest steps achieved during the last five years. Currently, the domain is divided into ten phyla and two main superphyla (TACK and DPANN) (Zuo et al., 2015). Initially, archaea were only found in extreme environments such as places with very high (up to 113 °C) and very low (down to −20 °C) temperatures as well as in environments with very high salinities (Barns et al., 1996; DeLong, 1998; Valentine, 2007). However, recent studies have frequently discovered them under non-extreme conditions and in high numbers under mesophilic conditions, including in the gastrointestinal tract of insects and mammals (recently reviewed by Moissl-Eichinger et al., 2017). Within the eukaryotic ecosystem, particularly methanogenic archaea are highly flexible in forming syntrophic interactions with a broad range of bacteria and are thus crucially involved in fermentation processes (Samuel and Gordon, 2006; Samuel et al., 2007). Despite their metabolic capabilities, information on archaea's cross-talk to their hosts, such as immunological response, is generally rare – most probably due to the fact that no archaeal pathogen has been described so far (Bang and Schmitz, 2015).

With respect to the human microbiome, *Methanobrevibacter smithii*, identified in stool samples 35 years ago, was the first human-associated archaeal species detected (Miller et al., 1982) and it is also the most abundant. It is known to comprise approximately 10% of all anaerobes within the human intestine and was found in nearly every human subject in a representative dataset (Bäckhed et al., 2005; Ley et al., 2005; Dridi et al., 2009). Additional methanogenic archaea cultured from stool samples include *Methanobrevibacter oralis*, *Methanosphaera stadtmanae* as well as *Methanomassiliicoccus* sp., yet their abundance varies within different studies (Dridi et al., 2009, 2012). Due to the widespread usage of universal prokaryotic primers such as V1–V2 16S rDNA primers as the standard method, the archaeal diversity within the human microbiome is often not captured accurately (Eloe-Fadrosh et al., 2016), since their 16S rRNA gene is not necessarily amplified by the universal primers. However, due to the development and application of high-throughput sequencing analyses over the last years, the number of archaeal members detected in association with the human microbiota has rapidly increased, and currently numerous archaeal communities are reported at different human body sites (Dridi et al., 2011). In addition to the human intestine, archaeal strains have also been frequently found in the oral cavity (*Methanobrevibacter* sp. and *Methanomassiliicoccus* sp.) (Kulik et al., 2001; Vianna et al., 2006, 2008; Horz et al., 2012) and on the skin (Thaumarchaeota) (Probst et al., 2013). Data on archaea associated with other human body sites are still generally rare (Belay et al., 1990; Sundquist et al., 2007); however, knowledge on this will certainly increase as a result of archaea-specific detection methods during high-throughput analyses as recently demonstrated (Koskinen et al., 2017).

The molecular cross-talk between archaea associated with eukaryotes has rarely been evaluated until now. So far, published information has exclusively focused on human immune cells or mice (Blais-Lecours et al., 2011, 2014; Bang et al., 2014). Whereas experiments with human epithelial cells revealed high tolerance against the most common archaeal strains in the gut (*M. smithii* and *M. stadtmanae*), peripheral blood mononuclear cells (PMBCs) as well as monocyte-derived dendritic cells (moDCs) of healthy subjects responded with high pro-inflammatory cytokine release after exposure to *M. stadtmanae* (Blais-Lecours et al., 2011, 2014; Bang et al., 2014). The response of human immune cells to *M. stadtmanae* was shown to be phagocytosis-dependent and resulted in the maturation of moDCs, thus suggesting a subsequent adaptive immune activation (Bang et al., 2014). Due to the phagocytosis-dependence a specific intracellular pattern recognition receptor (PRR) was hypothesized to sense archaeal cell components in an endocytic compartment. Indeed, most recently, *M. stadtmanae* as well its purified RNA were identified as potent stimuli for the human immune system, through recognition by TLR7 and TLR8 (Vierbuchen et al., 2017). Besides, evidence for archaea-specific monoclonal antibodies had already been obtained in earlier studies (Conway de Macario et al., 1982, 1983, 1984) and was confirmed in more recent studies (Yamabe et al., 2008; Blais-Lecours et al., 2011, 2014). Interestingly, one of those studies could demonstrate significant enhancement of strain-specific serum IgGs for *M. stadtmanae* in patients that suffered from inflammatory bowel diseases and whose stool was positive for this strain (Blais-Lecours et al., 2014). On the other hand, related strain-specific serum IgG-levels against the more common strain *M. smithii* were found independently of the abundance of this strain detected in the corresponding stool samples (Blais-Lecours et al., 2014). As summarized in Fig. 6, these results suggest not only a potential involvement

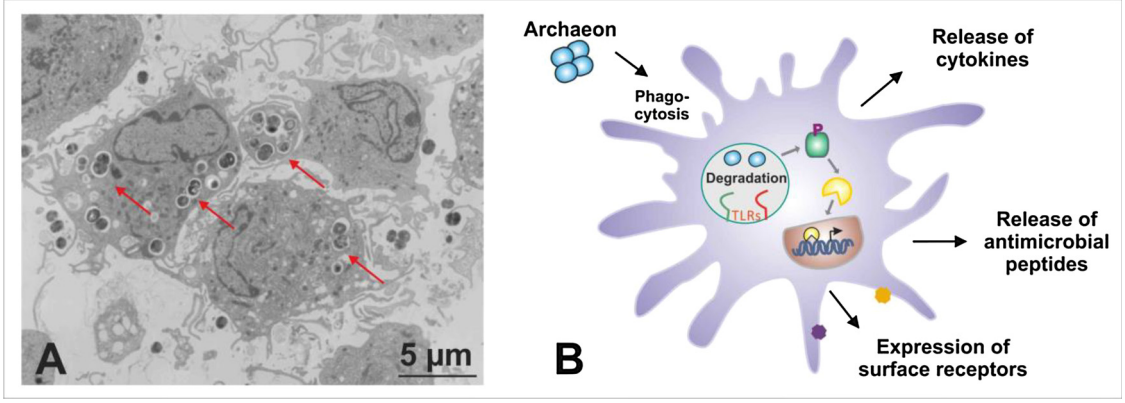

Fig. 6. Molecular cross-talk between archaea and human immune cells. (A) Monocyte-derived dendritic cells were stimulated with methanoarchaeal cells for a period of 4 h and then fixed for electron microscopy. Arrows indicate phagocytosed methanoarchaeal cells. (B) Schematic overview of the molecular cross-talk between archaea and human immune cells. Archaea are rapidly phagocytosed by human dendritic cells and subsequently degraded within the phagolysosome. Recognition of archaea via PRRs occurs after internal degradation and leads to the release of (pro- and anti-inflammatory) cytokines and antimicrobial peptides as well as to the activation of adaptive immune responses such as the expression of surface receptors.

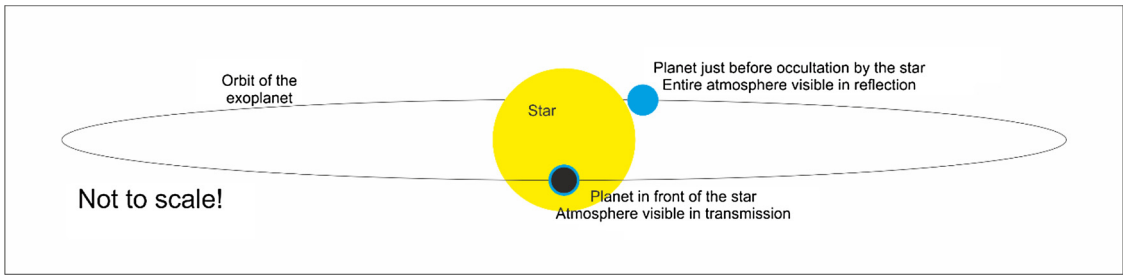

Fig. 7. The two most favorable constellations for the spectroscopy of an exoplanet's atmosphere (blue).

of *M. stadtmanae* in the establishment of inflammatory conditions involving the human gut, but also reveal strong evidence for differential cross-talk between various archaeal species and their (human) host as has been shown for numerous bacterial strains. Thus, it is conceivable that either more than one specific PRR is recognizing archaeal structures or that a few archaeal strains possess virulence factors, though there is no evidence for this to date.

Besides this immunologically driven cross-talk between archaea and their human host, several reports have demonstrated a high physiological impact of archaea during crucial fermentation processes in the gut. Particularly methanoarchaea are highly flexible in forming syntrophic interactions with a broad range of bacteria (primary and secondary fermenters) by using their products, like acetate, methanol, hydrogen and carbon dioxide (Thauer and Shima, 2006). A recent study showed that human-associated Methanomassiliicoccales strains are capable to degrade methylamines – known to potentially cause metabolic disorders – and thus might be an essential part of a healthy microbiota (Brugère et al., 2014). On the other hand, methanogenic archaea in the intestine produce methane as an end product, which has been shown to slow down the gut passage and support constipation as well as the development of obesity (Triantafyllou et al., 2014). Moreover, several studies proposed an indirect pathogenicity of archaea by promoting the growth of pathogenic bacteria (Conway de Macario and Macario, 2009). Recent studies also demonstrated a high immunological potential of the human gut-associated archaeon *M. stadtmanae* and proposed a role of this strain in the development of systemic intestinal inflammation (Blais-Lecours et al., 2011, 2014; Bang et al., 2014; Bang and Schmitz, 2015; Vierbuchen et al., 2017). Thus, additional studies on archaea as part of metaorganisms are urgently needed in order to answer the many open questions on their overall impact on the health and disease of their eukaryotic hosts. In order to expand our current knowledge, future studies should use state-of-the-art methods that cover archaeal diversity in samples of interest, because only if we take a look at the **whole** microbiome, can we learn from it!

11. Searching for metaorganisms on terrestrial planets – a future laboratory for astrophysicists and biologists

The last few decades have taught us under what unexpectedly extreme conditions life can exist on Earth. In all likelihood, however, the next few years and decades will give us the opportunity to search for and to investigate life under even (much) more extreme conditions, namely in planetary systems outside of the Solar System, and perhaps even on planets or moons within the Solar System. The latter, however, is not the topic of this contribution.

As early as in the 18th century, Swedenborg (1734), Kant (1755) and Laplace (1796) put forward the concept that the solar system was formed out of a clump of interstellar material. Under the conservation of angular momentum, this clump formed not only the Sun itself, but also a gaseous disk around it, out of which a planetary system evolved. The fact that in our solar system the eight major planets (and many of its less massive members) orbit the sun with rather small orbital inclinations relative to a single plane, though at very different distances from the sun, is direct evidence of this concept. Since the second half of the 20th century, with the advent of powerful computing, this so-called *nebular hypothesis* of our planetary system's origin can also be quantitatively modelled. These numerical simulations show that planets around stars are a normal outcome of star formation rather than a rare exception (for a state-of-the-art description of our current understanding of star and planet formation, see, e.g., Kippenhahn et al., 2012).

Finally, in the middle of the 1990s, the first planets around stars other than the Sun, so-called *exoplanets*, were found (Mayor and Queloz, 1995), and in the meantime several thousands of them have been confirmed, with more than one planet in many of the systems (for a daily updated list, see http://exoplanets.eu). As planets, they do not emit energy themselves but reflect radiation from their central star.[1] The combination of the ensuing small luminosity and the apparent very close proximity to the star leads to a luminosity contrast between exoplanet and star that, as yet, makes a direct observation of exoplanets impossible in the vast majority of cases. There is, however, an indirect way (Fig. 7). Simply on statistical grounds, in some cases the orbital plane of an exoplanet is oriented in such a way that, from our point of view, the exoplanet, on its way around the star, moves in front of the latter. In that situation, the planet faces the star with its illuminated side and shows us the dark side, leading to the occultation of a small part of the star. The ensuing temporary small decline of the star's brightness can thus be used as a technique for detecting exoplanets. In our context, however, these occultations also make an analysis of the planetary atmosphere (if present) possible. While the planet moves in front of the star, the main body of the planet not only occults part of the star. Along with it moves the exoplanet's atmosphere. The light of the star will radiate through the transparent parts of that atmosphere. A comparison of spectra of the star with and without the planet and atmosphere in front of it will allow for the determination of spectral contributions originating from the atmosphere of the planet. The advantage of this technique is that a spatial resolution neither of the star nor of the planet is required. The difficulty is rather that the projected size of the planet in front of the star is very small; in the case of the Earth in front of the Sun, seen from another planetary system, it would be $8{\cdot}10^{-5}$ of the star's radiating area. This is even more true for a planet's atmosphere; again in the Earth–Sun configuration with a characteristic thickness of the atmosphere of 100 km, it would be only $3{\cdot}10^{-6}$ of the star's radiating area. These numbers depend only on the relative sizes of the exoplanet, the star, and the atmosphere, not on the distance between the two, so long as it is a lot smaller than the distance from the observer, which is true in all possible cases (by many orders of magnitude). In the next few years, spectrographs will become available at all the telescopes which will make such transmission spectroscopy of planetary atmospheres routinely possible.

A second very favorable position occurs just before or immediately

[1] A few exceptions are known, like Jupiter, the biggest and most massive planet of the Solar System. Jupiter releases gravitational energy by very slowly contracting, an indication that the formation of this planet is not yet completed. Such exceptions, however, seem to be rather rare and do not influence the reasoning given here.

after the planet's own occultation, i.e., when it moves behind the star (Fig. 7). In those moments the planet turns its entirely illuminated side towards us and allows for the spectroscopy of the stellar light reflected by its atmosphere. The contribution of that signal to the total light of the system star–planet depends on the reflectivity of the planet's atmosphere, the relative sizes of planet and star, and the distance of the planet from the star. Knowledge of the uncontaminated stellar spectrum then allows for a derivation of the exoplanet's atmospheric reflection spectrum.

Once either one or both of these approaches of the spectroscopic investigation of exoplanetary atmospheres become routinely available – and this will be the case very soon, in all likelihood – an Eldorado for biologists and astrophysicists will open up which can only be fully exploited by a close collaboration between the two fields.

Astrophysicists have already determined the orbits of several thousand exoplanets. From this, we can estimate the general conditions on the surfaces of these planets, such as the expected temperature ranges, for instance. And from this, we can make statements about the possible habitability of individual planets. Habitability of a planet, in this context, usually refers to the type of life known to us, and requires the continuous presence of liquid water. Quite a number of potentially habitable planets are known already, even exoplanetary systems with several habitable planets. Interestingly enough, the closest star, Proxima Centauri, has a planet in its habitable zone (Anglada-Escudé et al., 2016). It is important, however, to be aware that habitability is only a necessary condition for the occurrence of life on an exoplanet, and far from a sufficient one. Moreover, the definition of habitability is a rather loose one, as, for instance, the true temperature on a planet depends not only on the incoming radiation from the star, but also very much on local conditions like mass, composition of the atmosphere, rotation of the exoplanet, inclination of its rotational axis relative to the orbital plane about the star, magnetic field, presence of moon(s), etc., most of which are as yet unknown. But in the near future we will be able to routinely provide spectra of exoplanetary atmospheres and test the local environment.

What do astrophysicists need from biologists? In order to analyze the spectra and to extract the desired information from them, we need to know what we have to look out for. This is important as, at least at the beginning, the relevant signals will be close to the detection limit. So we need to learn about the tracers of possible (simple) forms of life under the conditions prevailing on the exoplanets.

What can astrophysicists provide to biologists? We astrophysicists can provide an almost unlimited variety of spectra from planets throughout the universe. These will represent a vast variety of environments, different from each other in all respects, and many, if not most of them, very different from what we know on Earth.

Together, by combining our expertise, we will be able to investigate life outside of our planet, if it exists at all. If so, we may discover where life exists and where it does not (if we recognize it as such). We may be able to determine under what other conditions (our form of) life can exist.

Initially, we will have to concentrate on the nearer systems, because of their higher brightness. Right at the beginning we will have to determine whether life exists on exoplanets at all. And at the beginning we will be restricted to the most prominent cases because of the week signal and the ensuing unfavorable signal-to-noise ratio. But it will only be a matter of time to resolve these issues.

12. Important areas for future research

The increasing realization that organisms exist only as metaorganisms has led to three important insights necessary for understanding metaorganism adapation in extreme environments. First, an in-depth understanding of the adaptation, physiology, and development of a given host species requires that it must not be studied in isolation. Second, the health and fitness of a metaorganism depend on its modularity that allows the change or exchange of parterns. This view is consistent with the "plasticity first" model of evolution, which states that plasticity can precede and facilitate evolutionary adaptation (Levis and Pfennig, 2016). Finally, the holobiont or metaorganism may be an important unit of evolutionary selection, a selection of "teams" containing many genomes and species. These unexpected insights require new research initiatives to systematically evaluate the critical position of microbes in the metaorganism's adaptation. Despite the recent advances in our understanding of commensal colonization, competition, and impact on immune cell development and differentiation (Bosch, 2014), many aspects of the host–microbe interaction remain unknown. Important areas of future research now include developing approaches to examine at a mechanistic level how a complex microbiota interacts as a spatially and temporally dynamic network.

Microbial symbionts represent a specific form of genetic inheritance, which has often been acquired vertically, either through the egg or from the maternal environment (Moran et al., 2008; Gilbert et al., 2010; Funkhouser and Bordenstein, 2013). Genetic variation in the symbionts can produce phenotypic variation of the metaorganism and may impact the ecological tolerance and distribution of the host. For instance, symbiotic bacteria in pea aphids provide selectable allelic variation (e.g., thermotolerance, color, and parasitoid resistance) that enables the host to better persist under different environmental conditions (Oliver et al., 2009; Tsuchida et al., 2010; Moran and Yun, 2015).

Overall, these findings suggest a possible evolutionary process whereby populations become increasingly reproductively isolated through the divergence of their microbiomes. Symbionts are also thought to be involved in major transitions in the history of life. The endosymbiotic theory of eukaryotic cell formation holds that the origin of eukaryotic life began through the merging of archaea and bacterial cells and genes (Margulis, 1981). Similarly, animal multicellularity might have emerged from the symbiosis of a choanoflagellate protist with a particular bacterial partner (e.g., Alegado et al., 2012). Another evolutionary transition, the origin of placental mammals, may have been promoted by symbiosis, namely, through the incorporation of retroviruses from other organisms. These retroviruses, which contain their own enhancer elements, appear to have allowed the rewiring of cell circuitry to produce the progesterone-responsive uterine decidual cell (Lynch et al., 2015). This particular role of beneficial microbes in eukaryotic development points to the complexity of genetic interrelations within the metaorganism species community. Taken together, symbionts are critical to normal development, fitness and natural selection. They help generate organs, they can produce selectable variant phenotypes, they can create the conditions for reproductive isolation, they are crucial for the fitness of their eukaryotic hosts under changing environmental condition, and they may be the facilitators of evolutionary transitions. Symbiotic relationships are the signature of life on earth, and evolutionary biology has to include the species community within the metaorganism as a central unit of selection. "Biology has entered a new era with the capacity to understand that an organism's genetics and fitness are inclusive of its microbiome" (Brucker and Bordenstein, 2014). The past few years have seen a remarkable demonstration of the role of microbiota for multicellular host functions, but what is needed now is a sound understanding of the molecules and mechanisms driving this role and then capitalizing on this knowledge to improve health and decrease disease (Waldor et al., 2015).

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References

Abe, T., Bignell, D., Higashi, M. (Eds.), 2000. Termites: Evolution, Sociality, Symbioses, Ecology. Springer Science & Business Media, New York.

Adam, P.S., Borrel, G., Brochier-Armanet, C., Gribaldo, S., 2017. The growing tree of Archaea: new perspectives on their diversity, evolution and ecology. ISME J. 11, 2407–2425.

Alegado, R.A., Brown, L.W., Cao, S., Dermenjian, R.K., Zuzow, R., Fairclough, S.R., Clardy, J., King, N., 2012. A bacterial sulfonolipid triggers multicellular development in the closest living relatives of animals. eLife 1 e00013.

Allison, S.D., Martiny, J.B.H., 2008. Resistance, resilience, and redundancy in microbial communities. Proc. Natl. Acad. Sci. USA 105, 11512–11519.

Aminov, R.I., 2011. Horizontal gene exchange in environmental microbiota. Front. Microbiol. 2, 158.

Anglada-Escudé, G., Amado, P.J., Barnes, J., Berdiñas, Z.M., Butler, R.P., Coleman, G.A.L., Cueva, I., Dreizler, S., Endl, M., Giesers, B., Jeffers, S.V., Jenkins, J.S., Jones, H.R.A., Kiraga, M., Kürster, M., López-González, M.J., Marvin, C.J., Morales, N., Morin, J., Nelson, R.P., Ortiz, J.L., Ofir, A., Paardekooper, S.-J., Reiners, A., Rodríguez, E., Rodríguez-López, C., Sarmiento, L.F., Strachan, J.P., Tsapras, Y., Tuomi, M., Zechmeister, M., 2016. A terrestrial planet candidate in a temperate orbit around Proxima Centauri. Nature 536, 437–440.

Bäckhed, F., Ley, R.E., Sonnenburg, J.L., Peterson, D.A., Gordon, J.I., 2005. Host–bacterial mutualism in the human intestine. Science 307, 1915–1920.

Baker, D.M., Andras, J.P., Jordán-Garza, A.G., Fogel, M.L., 2013. Nitrate competition in a coral symbiosis varies with temperature among *Symbiodinium* clades. ISME J. 7, 1248–1251.

Bano, A., Fatima, M., 2009. Salt tolerance in *Zea mays* (L.) following inoculation with *Rhizobium* and *Pseudomonas*. Biol. Fert. Soils 45, 405–413.

Bang, C., Schmitz, R.A., 2015. Archaea associated with human surfaces: not to be underestimated. FEMS Microbiol. Rev. 39, 631–648.

Bang, C., Weidenbach, K., Gutsmann, T., Heine, H., Schmitz, R.A., 2014. The intestinal archaea *Methanosphaera stadtmanae* and *Methanobrevibacter smithii* activate human dendritic cells. PloS ONE 9, e99411.

Barns, S.M., Delwiche, C.F., Palmer, J.D., Pace, N.R., 1996. Perspectives on archaeal diversity, thermophily and monophyly from environmental rRNA sequences. Proc. Natl. Acad. Sci. USA 93, 9188–9193.

Barroso-Batista, J., Sousa, A., Lourenço, M., Bergman, M.-L., Sobral, D., Demengeot, J., Xavier, K.B., Gordo, I., 2014. The first steps of adaptation of *Escherichia coli* to the gut are dominated by soft sweeps. PLoS Genet. 10, e1004182.

Barshis, D.J., Ladner, J.T., Oliver, T.A., Seneca, F.O., Traylor-Knowles, N., Palumbi, S.R., 2013. Genomic basis for coral resilience to climate change. Proc. Natl. Acad. Sci. USA 110, 1387–1392.

Barshis, D.J., Ladner, J.T., Oliver, T.A., Palumbi, S.R., 2014. Lineage-specific transcriptional profiles of *Symbiodinium* spp. unaltered by heat stress in a coral host. Mol. Biol. Evol. 31, 1343–1352.

Bassler, B.L., 2002. Small talk. Cell-to-cell communication in bacteria. Cell 109, 421–424.

Bassler, B., 2015. Manipulating quorum sensing to control bacterial pathogenicity. FASEB J. 29 (Suppl. 88.1).

Bauer, W.D., Mathesius, U., 2004. Plant responses to bacterial quorum sensing signals. Curr. Opin. Plant Biol. 7, 429–433.

Bay, R.A., Palumbi, S.R., 2014. Multilocus adaptation associated with heat resistance in reef-building corals. Curr. Biol. 24, 2952–2956.

Bay, R.A., Palumbi, S.R., 2015. Rapid acclimation ability mediated by transcriptome changes in reef-building corals. Genome Biol. Evol. 7, 1602–1612.

Belay, N., Mukhopadhyay, B., Conway de Macario, E., Galask, R., Daniels, L., 1990. Methanogenic bacteria in human vaginal samples. J. Clin. Microbiol. 28, 1666–1668.

Bell, J.J., 2008. Sponges as agents of biological disturbance. MEPS 368, 127–135.

Benavides, M., Houlbrèque, F., Camps, M., Lorrain, A., Grosso, O., Bonnet, S., 2016. Diazotrophs: a non-negligible source of nitrogen for the tropical coral *Stylophora pistillata*. J. Exp. Biol. 219, 2608–2612.

Bennett, G.M., Moran, N.A., 2015. Heritable symbiosis: the advantages and perils of an evolutionary rabbit hole. Proc. Natl. Acad. Sci. USA 112, 10169–10176.

Bhattacharya, D., Agrawal, S., Aranda, M., Baumgarten, S., Belcaid, M., Drake, J.L., Erwin, D., Foret, S., Gates, R.D., Gruber, D.F., Kamel, B., Lesser, M.P., Levy, O., Liew, Y.J., MacManes, M., Mass, T., Medina, M., Mehr, S., Meyer, E., Price, D.C., Putnam, H.M., Qiu, H., Shinzato, C., Shoguchi, E., Stokes, A.J., Tambutté, S., Tchernov, D., Voolstra, C.R., Wagner, N., Walker, C.W., Weber, A.P.M., Weis, V., Zelzion, E., Zoccola, D., Falkowski, P.G., 2016. Comparative genomics explains the evolutionary success of reef-forming corals. Elife 5, e13288.

Bikel, S., Valdez-Lara, A., Cornejo-Granados, F., Rico, K., Canizales-Quinteros, S., Soberón, X., Del Pozo-Yauner, L., Ochoa-Leyva, A., 2015. Combining metagenomics, metatranscriptomics and viromics to explore novel microbial interactions: towards a systems-level understanding of human microbiome. Comput. Struct. Biotechnol. J. 13, 390–401.

Bilton, D., Paula, J., Bishop, J., 2002. Dispersal, genetic differentiation and speciation in estuarine organisms. Estuar. Coast. Shelf Sci. 55, 937–952.

Birkeland, C., 1997. Life and Death of Coral Reefs. Springer Science, New York.

Blais-Lecours, P., Duchaine, C., Taillefer, M., Tremblay, C., Veillette, M., Cormier, Y., Marsolais, D., 2011. Immunogenic properties of archaeal species found in bioaerosols. PLoS One 6, e23326.

Blais-Lecours, P., Marsolais, D., Cormier, Y., Berberi, M., Haché, C., Bourdages, R., Duchaine, C., 2014. Increased prevalence of *Methanosphaera stadtmanae* in inflammatory bowel diseases. PloS One 9, e87734.

Blaser, M.J., 2016. Antibiotic use and its consequences for the normal microbiome. Science 352, 544–545.

Bordenstein, S.R., Theis, K.R., 2015. Host biology in light of the microbiome: ten principles of holobionts and hologenomes. PLoS Biol. 13, e1002226.

Bosch, T.C.G., 2012. What *Hydra* has to say about the role and origin of symbiotic interactions. Biol. Bull. 223, 78–84.

Bosch, T.C.G., 2013. Cnidarian–microbe interactions and the origin of innate immunity in metazoans. Ann. Rev. Microbiol. 67, 499–518.

Bosch, T.C.G., 2014. Rethinking the role of immunity: lessons from *Hydra*. Trends Immunol. 35, 495–502.

Bosch, T.C.G., McFall-Ngai, M.J., 2011. Metaorganisms as the new frontier. Zoology 114, 185–190.

Brito, I.L., Yilmaz, S., Huang, K., Xu, L., Jupiter, S.D., Jenkins, A.P., Naisilisili, W., Tamminen, M., Smillie, C.S., Wortman, J.R., Birren, B.W., Xavier, R.J., Blainey, P.C., Singh, A.K., Gevers, D., Alm, E.J., 2016. Mobile genes in the human microbiome are structured from global to individual scales. Nature 535, 435–439.

Brown, B.E., Dunne, R.P., Scoffin, T.P., Le Tissier, M.D.A., 1994. Solar damage in intertidal corals. Mar. Ecol. Prog. Ser. 105, 219–230.

Brucker, R.M., Bordenstein, S.R., 2014. Response to Comment on "The hologenomic basis of speciation: gut bacteria cause hybrid lethality in the genus Nasonia". Science 345, 1011.

Brugère, J.F., Borrel, G., Gaci, N., Tottey, W., O'Toole, P.W., Malpuech-Brugère, C., 2014. Archaebiotics: proposed therapeutic use of archaea to prevent trimethylaminuria and cardiovascular disease. Gut Microbes 5, 5–10.

Brüwer, J.D., Voolstra, C.R., 2017. Insights into viral community composition of the cnidarian model metaorganism *Aiptasia* using RNA-Seq data. PeerJ Preprints 5, e3343v1.

Brüwer, J.D., Agrawal, S., Liew, Y.J., Aranda, M., Voolstra, C.R., 2017. Association of coral algal symbionts with a diverse viral community responsive to heat shock. BMC Microbiol. 17, 174.

Brune, A., 2014. Symbiotic digestion of lignocellulose in termite guts. Nat. Rev. Microbiol. 12, 168–180.

Brussaard, C.P.D., 2004. Viral control of phytoplankton populations – a review. J. Eukaryot. Microbiol. 51, 125–138.

Buddemeier, R.W., Fautin, D.G., 1993. Coral bleaching as an adaptive mechanism – a testable hypothesis. Bioscience 43, 320–326.

Cárdenas, A., Meyer, F., Schwieder, H., Wild, C., Gärdes, A., 2015. The formation of aggregates in coral reef waters under elevated concentrations of dissolved inorganic and organic carbon: a mesocosm approach. Mar. Chem. 175, 47–55.

Cardini, U., Bednarz, V.N., Naumann, M.S., van Hoytema, N., Rix, L., Foster, R.A., Al-Rshaidat, M.M.D., Wild, C., 2015. Functional significance of dinitrogen fixation in sustaining coral productivity under oligotrophic conditions. Proc. R. Soc. B Biol. Sci. 282, 20152257.

Cardini, U., Bednarz, V.N., van Hoytema, N., Rovere, A., Naumann, M.S., Al-Rshaidat, M.M.D., Wild, C., 2016. Budget of primary production and dinitrogen fixation in a highly seasonal Red Sea coral reef. Ecosystems 19, 771–785.

Castillo, A., 2015. How bacteria use quorum sensing to communicate. Nature Education 8, 4.

Castillo-Juárez, I., Maeda, T., Mandujano-Tinoco, E.A., Tomás, M., Pérez-Eretza, B., García-Contreras, S.J., Wood, T.K., García-Contreras, R., 2015. Role of quorum sensing in bacterial infections. World J. Clin. Cases 3, 575–598.

Cavanaugh, C.M., Gardiner, S.L., Jones, M.L., Jannasch, H.W., Waterbury, J.B., 1981. Prokaryotic cells in the hydrothermal vent tube worm *Riftia pachyptila* Jones: possible chemoautotrophic symbionts. Science 213, 340–342.

Cavicchioli, R., 2007. Archaea: Cellular and Molecular Biology. ASM Press, Washington, D.C.

Connell, J.H., 1978. Diversity in tropical rain forests and coral reefs. Science 199, 1302–1310.

Conway de Macario, E., Macario, A.J.L., 2009. Methanogenic archaea in health and disease: a novel paradigm of microbial pathogenesis. Int. J. Med. Microbiol. 299, 99–108.

Conway de Macario, E., Macario, A.J., Kandler, O., 1982. Monoclonal antibodies for immunochemical analysis of methanogenic bacteria. J. Immunol. 129, 1670–1674.

Conway de Macario, E., Macario, A.J., Magariños, M.C., König, H., Kandler, O., 1983. Dissecting the antigenic mosaic of the archaebacterium *Methanobacterium thermoautotrophicum* by monoclonal antibodies of defined molecular specificity. Proc. Natl. Acad. Sci. USA 80, 6346–6350.

Conway de Macario, E., König, H., Macario, A.J., Kandler, O., 1984. Six antigenic determinants in the surface layer of the archaebacterium *Methanococcus vannielii* revealed by monoclonal antibodies. J. Immunol. 132, 883–887.

Corradi, N., Bonfante, P., 2012. The arbuscular mycorrhizal symbiosis: origin and evolution of a beneficial plant infection. PLoS Pathog. 8, e1002600.

Cunning, R., Baker, A.C., 2012. Excess algal symbionts increase the susceptibility of reef corals to bleaching. Nat. Clim. Chang. 3, 259–262.

Cunning, R., Muller, E.B., Gates, R.D., Nisbet, R.M., 2017. A dynamic bioenergetic model for coral–*Symbiodinium* symbioses and coral bleaching as an alternate stable state. J. Theor. Biol. 431, 49–62.

Darling, J.A., Reitzel, A.M., Finnerty, J.R., 2004. Regional population structure of a widely introduced estuarine invertebrate: *Nematostella vectensis* Stephenson in New England. Mol. Ecol. 13, 2969–2981.

Darwin, C., 1842. The Structure and Distribution of Coral Reefs. Smith Elder and Co., London.

De Goeij, J.M., van Oevelen, D., Vermeij, M.J.A., Osinga, R., Middelburg, J.J., de Goeij, A.F.P.M., Admiraal, W., 2013. Surviving in a marine desert: the sponge loop retains resources within coral reefs. Science 342, 108–110.

De Rosa, M., Gambacorta, A., Gliozzi, A., 1986. Structure, biosynthesis, and physicochemical properties of archaebacterial lipids. Microbiol. Rev. 50, 70–80.

De Zelicourt, A., Al-Yousif, M., Hirt, H., 2013. Rhizosphere microbes as essential partners

for plant stress tolerance. Mol. Plant 6, 242–245.
DeLong, E.F., 1998. Everything in moderation: Archaea as 'non-extremophiles'. Curr. Opin. Genet. Developm. 8, 649–654.
DeMartini, E.E., Friedlander, A.M., Sandin, S.A., Sala, E., 2008. Differences in fish-assemblage structure between fished and unfished atolls in the northern Line Islands, central Pacific. Mar. Ecol. Prog. Ser. 365, 199–215.
Deines, P., Lachnit, T., Bosch, T.C.G., 2017. Competing forces maintain the *Hydra* metaorganism. Immunol Rev. 279, 123–136.
Denamur, E., Matic, I., 2006. Evolution of mutation rates in bacteria. Mol. Microbiol. 60, 820–827.
Douglas, A.E., 1998. Nutritional interactions in insect–microbial symbioses: aphids and their symbiotic bacteria *Buchnera*. Annu. Rev. Entomol. 43, 17–37.
Dridi, B., Henry, M., El Khéchine, A., Raoult, D., Drancourt, M., 2009. High prevalence of *Methanobrevibacter smithii* and *Methanosphaera stadtmanae* detected in the human gut using an improved DNA detection protocol. PLoS One 4, e7063.
Dridi, B., Raoult, D., Drancourt, M., 2011. Archaea as emerging organisms in complex human microbiomes. Anaerobe 17, 56–63.
Dridi, B., Henry, M., Richet, H., Raoult, D., Drancourt, M., 2012. Age-related prevalence of *Methanomassiliicoccus luminyensis* in the human gut microbiome. APMIS 120, 773–777.
Dubilier, N., Bergin, C., Lott, C., 2008. Symbiotic diversity in marine animals: the art of harnessing chemosynthesis. Nature Rev. Microbiol. 6, 725–740.
Edgar, R.C., 2004. MUSCLE: multiple sequence alignment with high accuracy and high throughput. Nucleic Acids Res. 32, 1792–1797.
Egamberdieva, D., Kucharova, Z., 2009. Selection for root colonizing bacteria stimulating wheat growth in saline soils. Biol. Fert. Soil. 45, 563–571.
Eloe-Fadrosh, E.A., Ivanova, N.N., Woyke, T., Kyrpides, N.C., 2016. Metagenomics uncovers gaps in amplicon-based detection of microbial diversity. Nature Microbiol. 1, 15032.
Falkowski, P.G., Dubinsky, Z., Muscatine, L., Porter, J.W., 1984. Light and the bioenergetics of a symbiotic coral. Bioscience 34, 705–709.
Falkowski, P.G., Dubinsky, Z., Muscatine, L., McCloskey, L., 1993. Population control in symbiotic corals. Bioscience 43, 606–611.
Fiore, C.L., Jarett, J.K., Olson, N.D., Lesser, M.P., 2010. Nitrogen fixation and nitrogen transformations in marine symbioses. Trends Microbiol. 18, 455–463.
Fraune, S., Bosch, T.C.G., 2010. Why bacteria matter in animal development and evolution. BioEssays 32, 571–580.
Fraune, S., Anton-Erxleben, F., Augustin, R., Franzenburg, S., Knop, M., Schröder, K., Willoweit-Ohl, D., Bosch, T.C.G., 2014. Bacteria–bacteria interactions within the microbiota of the ancestral metazoan *Hydra* contribute to fungal resistance. ISME J. 9, 1543–1556.
Fraune, S., Forêt, S., Reitzel, A., 2016. Using *Nematostella vectensis* to study the interactions between genome, epigenome, and bacteria in a changing environment. Front. Mar. Sci. 3, 148.
Freeman, S., Horowitz, S., Sharon, A., 2001. Pathogenic and nonpathogenic lifestyles in *Colletotrichum acutatum* from strawberry and other plants. Phytopathology 91, 986–992.
French, J.R., Turner, G.L., Bradbury, J.F., 1976. Nitrogen fixation by bacteria from the hindgut of termites. J. Gen. Microbiol. 96, 202–206.
Funkhouser, L.J., Bordenstein, S.R., 2013. Mom knows best: the universality of maternal microbial transmission. PLoS Biol. 11, e1001631.
Fuqua, W.C., Winans, S.C., Greenberg, E.P., 1994. Quorum sensing in bacteria: the LuxR-LuxI family of cell density-responsive transcriptional regulators. J. Bacteriol. 176, 269–275.
Gates, R.D., Hoegh-Guldberg, O., McFall-Ngai, M.J., Bil, K.Y., Muscatine, L., 1995. Free amino acids exhibit anthozoan "host factor" activity: they induce the release of photosynthate from symbiotic dinoflagellates in vitro. Proc. Natl. Acad. Sci. USA 92, 7430–7434.
Gerba, C.P., Betancourt, W.Q., 2017. Viral aggregation: impact on virus behavior in the environment. Environ. Sci. Technol. 51, 7318–7325.
Geurts, R., Lillo, A., Bisseling, T., 2012. Exploiting an ancient signalling machinery to enjoy a nitrogen fixing symbiosis. Curr. Opin. Plant Biol. 15, 438–443.
Gilbert, S.F., McDonald, E., Boyle, N., Buttino, N., Gyi, L., Mai, M., Prakash, N., Robinson, J., 2010. Symbiosis as a source of selectable epigenetic variation: taking the heat for the big guy. Phil. Trans. R. Soc. B 365, 671–678.
Gilbert, S.F., Sapp, J., Tauber, A.I., 2012. A symbiotic view of life: we have never been individuals. Q. Rev. Biol. 87, 325–341.
Gilbert, J.A., Quinn, R.A., Debelius, J., Xu, Z.Z., Morton, J., Garg, N., Jansson, J.K., Dorrestein, P.C., Knight, R., 2016. Microbiome-wide association studies link dynamic microbial consortia to disease. Nature 535, 94–103.
Givskov, M., de Nys, R., Manefield, M., Gram, L., Maximilien, R., Eberl, L., Molin, S., Steinberg, P.D., Kjelleberg, S., 1996. Eukaryotic interference with homoserine lactone-mediated prokaryotic signalling. J. Bacteriol. 178, 6618–6622.
Goodrich, J.K., Waters, J.L., Poole, A.C., Sutter, J.L., Koren, O., Blekhman, R., Beaumont, M., Van Treuren, W., Knight, R., Bell, J.T., Spector, T.D., Clark, A.G., Ley, R.E., 2014. Human genetics shape the gut microbiome. Cell 159, 789–799.
Gove, J.M., McManus, M.A., Neuheimer, A.B., Polovina, J.J., Drazen, J.C., Smith, C.R., Merrifield, M.A., Friedlander, A.M., Ehses, J.S., Young, C., Dillon, A.K., Williams, G.J., 2015. Near-island biological hotspots in barren ocean basins. Nat. Commun. 7, 1–34.
Grandclément, C., Tannières, M., Moréra, S., Dessaux, Y., Faure, D.D., 2016. Quorum quenching: role in nature and applied developments. FEMS Microbiol. Rev. 40, 86–116.
Grasis, J.A., Lachnit, T., Anton-Erxleben, F., Lim, Y.W., Schmieder, R., Fraune, S., Franzenburg, S., Insua, S., Machado, G., Haynes, M., Little, M., Kimble, R., Rosenstiel, P., Rohwer, F.L., Bosch, T.C.G., 2014. Species-specific viromes in the ancestral holobiont hydra. PLoS One 9, e109952.
Grottoli, A.G., Dalcin Martins, P., Wilkins, M.J., Johnston, M.D., Warner, M.E., Cai, W.J., Melman, T.F., Hoadley, K.D., Pettay, D.T., Levas, S., Schoepf, V., 2018. Coral physiology and microbiome dynamics under combined warming and ocean acidification. PLOS One 13, e0191156.
Habetha, M., Anton-Erxleben, F., Neumann, K., Bosch, T.C.G., 2003. The *Hydra viridis/Chlorella* symbiosis: growth and sexual differentiation in polyps without symbionts. Zoology 106, 101–108.
Hand, C., Uhlinger, K.R., 1994. The unique, widely distributed, estuarine sea anemone, *Nematostella vectensis* Stephenson: a review, new facts, and questions. Estuaries 17, 501–508.
Hand, C., Uhlinger, K., 1995. Asexual reproduction by transverse fission and some anomalies in the sea anemone *Nematostella vectensis*. Invertebr. Biol. 114, 9–18.
Harms, K., Lunnan, A., Hülter, N., Mourier, T., Vinner, L., Andam, C.P., Marttinen, P., Fridholm, H., Hansen, A.J., Hanage, W.P., Nielsen, K.M., Willerslev, E., Johnsen, P.J., 2016. Substitutions of short heterologous DNA segments of intragenomic or extragenomic origins produce clustered genomic polymorphisms. Proc. Natl. Acad. Sci. USA 113, 15066–15071.
Hatcher, B.G., 1990. Coral reef primary productivity. A hierarchy of pattern and process. Trends Ecol. Evol. 5, 149–155.
Hentschel, U., Piel, J., Degnan, S.M., Taylor, M.W., 2012. Genomic insights into the marine sponge microbiome. Nature Rev. Microbiol. 10, 641–654.
Hema, M., Murali, A., Ni, P., Vaughan, R.C., Fujisaki, K., Tsvetkova, I., Dragnea, B., Kao, C.C., 2010. Effects of amino-acid substitutions in the brome mosaic virus capsid protein on RNA encapsidation. Mol. Plant -Microbe Interact. 23, 1433–1447.
Hill, M., Hill, A., 2012. The magnesium inhibition and arrested phagosome hypotheses: new perspectives on the evolution and ecology of *Symbiodinium* symbioses. Biol. Rev. 87, 804–821.
Hooper, L.V., Wong, M.H., Thelin, A., Hansson, L., Falk, P.G., Gordon, J.I., 2001. Molecular analysis of commensal host–microbial relationships in the intestine. Science 291, 881–884.
Horz, H.P., Seyfarth, I., Conrads, G., 2012. McrA and 16S rRNA gene analysis suggests a novel lineage of *Archaea* phylogenetically affiliated with Thermoplasmatales in human subgingival plaque. Anaerobe 18, 373–377.
Hsiao, E.Y., McBride, S.W., Hsien, S., Sharon, G., Hyde, E.R., McCue, T., Codelli, J.A., Chow, J., Reisman, S.E., Petrosino, J.F., Patterson, P.H., Mazmanian, S.K., 2013. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell 155, 1451–1463.
Hughes, T.P., Baird, A.H., Bellwood, D.R., Card, M., Connolly, S.R., Folke, C., Grosberg, R., Hoegh-Guldberg, O., Jackson, J.B.C., Kleypas, J., Lough, J.M., Marshall, P., Nyström, M., Palumbi, S.J., Pandolfi, J.M., Rosen, B., Roughgarden, J., 2003. Climate change, human impacts, and the resilience of coral reefs. Science 301, 929–933.
Hughes, T.P., Kerry, J.T., Álvarez-Noriega, M., Álvarez-Romero, J.G., Anderson, K.D., Baird, A.H., Babcock, R.C., Beger, M., Bellwood, D.R., Berkelmans, R., Bridge, T.C., Butler, I.R., Byrne, M., Cantin, N.E., Comeau, S., Connolly, S.R., Cumming, G.S., Dalton, S.J., Diaz-Pulido, G., Eakin, C.M., Figueira, W.F., Gilmour, J.P., Harrison, H.B., Heron, S.F., Hoey, A.S., Hobbs, J.-P.A., Hoogenboom, M.O., Kennedy, E.V., Kuo, C., Lough, J.M., Lowe, R.J., Liu, G., McCulloch, M.T., Malcolm, H.A., McWilliam, M.J., Pandolfi, J.M., Pears, R.J., Pratchett, M.S., Schoepf, V., Simpson, T., Skirving, W.J., Sommer, B., Torda, G., Wachenfeld, D.R., Willis, B.L., Wilson, S.K., 2017. Global warming and recurrent mass bleaching of corals. Nature 543, 373–377.
Hughes, T.P., Anderson, K.D., Connolly, S.R., Heron, S.F., Kerry, J.T., Lough, J.M., Baird, A.H., Baum, J.K., Berumen, M.L., Bridge, T.C., Claar, D.C., Eakin, C.M., Gilmour, J.P., Graham, N.A.J., Harrison, H., Hobbs, J.A., Hoey, A.S., Hoogenboom, M., Lowe, R.J., Mcculloch, M.T., Pandolfi, J.M., Pratchett, M., Schoepf, V., Torda, G., Wilson, S.K., 2018. Spatial and temporal patterns of mass bleaching of corals in the Anthropocene. Science 83, 80–83.
Hume, B.C., Voolstra, C.R., Arif, C., D'Angelo, C., Burt, J.A., Eyal, G., Loya, Y., Wiedenmann, J., 2016. Ancestral genetic diversity associated with the rapid spread of stress-tolerant coral symbionts in response to Holocene climate change. Proc. Natl. Acad. Sci. USA 113, 4416–4421.
Imhof, M., Schlötterer, C., 2001. Fitness effects of advantageous mutations in evolving *Escherichia coli* populations. Proc. Natl. Acad. Sci. USA 98, 1113–1117.
Ismail, A.S., Valastyan, J.S., Bassler, B.L., 2016. A host-produced autoinducer-2 mimic activates bacterial quorum sensing. Cell Host Microbe 19, 470–480.
Jahn, M.T., Markert, S.M., Ryu, T., Ravasi, T., Stigloher, C., Hentschel, U., Moitnho-Silva, L., 2016. Shedding light on cell compartmentation in the candidate phylum Poribacteria by high resolution visualisation and transcriptional profiling. Sci. Rep. 6, 35860.
Joint, I., Tait, K., Callow, M.E., Callow, J.A., Milton, D., Williams, P., Cámara, M., 2002. Cell-to-cell communication across the prokaryote–eukaryote boundary. Science 298, 1207.
Jones, C.G., Lawton, J.H., Shachak, M., Jones, C.G., Lawton, J.H., Shachak, M., 2008. Organisms as ecosystem engineers. Oikos 69, 373–386.
Joseph, C.M., Phillips, D.A., 2003. Metabolites from soil bacteria affect plant water relations. Plant Physiol. Biochem. 41, 189–192.
Justice, S.S., Hunstad, D.A., Cegelski, L., Hultgren, S.J., 2008. Morphological plasticity as a bacterial survival strategy. Nat. Rev. Microbiol. 6, 162–168.
Kalia, V.C., 2015. Quorum Sensing vs Quorum Quenching: A Battle with No End in Sight. Springer India, New Delhi.
Kanaani, J., Ginsburg, H., 1989. Metabolic interconnection between the human malarial parasite *Plasmodium falciparum* and its host erythrocyte. Regulation of ATP levels by means of an adenylate translocator and adenylate kinase. J. Biol. Chem. 264, 3194–3199.
Kandler, O., König, H., 1998. Cell wall polymers in Archaea (Archaebacteria). Cell. Molec. Life Sci. 54, 305–308.

Kant, I., 1755. Allgemeine Naturgeschichte und Theorie des Himmels. Petersen, Königsberg.
Keeling, P.J., Palmer, J.D., 2008. Horizontal gene transfer in eukaryotic evolution. Nat. Rev. Genet. 9, 605–618.
Kenkel, C.D., Matz, M.V., 2016. Gene expression plasticity as a mechanism of coral adaptation to a variable environment. Nature Ecol. Evol. 1, 0014.
Kenkel, C.D., Goodbody-Gringley, G., Caillaud, D., Davies, S.W., Bartels, E., Matz, M.V., 2013. Evidence for a host role in thermotolerance divergence between populations of the mustard hill coral (*Porites astreoides*) from different reef environments. Mol. Ecol. 22, 4335–4348.
King, N., 2004. The unicellular ancestry of animal development. Dev. Cell 7, 313–325.
Kippenhahn, R., Weigert, A., Weiss, A., 2012. Stellar Structure and Evolution, 2nd ed. Springer, Heidelberg.
Kiran, G.S., Hassan, S., Sajayan, A., Selvin, J., 2017. Quorum quenching compounds from natural sources. In: Sugathan, S., Pradeep, N.S., Abdulhameed, S. (Eds.), Bioresources and Bioprocess in Biotechnology, Vol. 2: Exploring Potential Biomolecules. Springer Nature Singapore, Singapore, pp. 351–364.
Koga, Y., Morii, H., 2005. Recent advances in structural research on ether lipids from archaea including comparative and physiological aspects. Biosci. Biotechnol. Biochem. 69, 2019–2034.
Koga, Y., Morii, H., 2007. Biosynthesis of ether-type polar lipids in archaea and evolutionary considerations. Microbiol. Molec. Biol. Rev. 71, 97–120.
Koga, Y., Nishihara, M., Morii, H., Akagawa-Matsushita, M., 1993. Ether polar lipids of methanogenic bacteria: structures, comparative aspects, and biosyntheses. Microbiol. Rev. 57, 164–182.
Koskinen, K., Pausan, M.R., Perras, A.K., Beck, M., Bang, C., Mora, M., Schilhabel, A., Schmitz, R., Moissl-Eichinger, C., 2017. First insights into the diverse human archaeome: specific detection of Archaea in the gastrointestinal tract, lung, and nose and on skin. mBio 8 e00824-17.
Kostic, A.D., Chun, E., Robertson, L., Glickman, J.N., Gallini, C.A., Michaud, M., Clancy, T.E., Chung, D.C., Lochhead, P., Hold, G.L., El-Omar, E.M., Brenner, D., Fuchs, C.S., Meyerson, M., Garrett, W.S., 2013. *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor–immune microenvironment. Cell Host Microbe 14, 207–215.
Kravchenko, V.V., Kaufmann, G.F., Mathison, J.C., Scott, D.A., Katz, A.Z., Grauer, D.C., Lehmann, M., Meijler, M.M., Janda, K.D., Ulevitch, R.J., 2008. Modulation of gene expression via disruption of NF-κB signaling by a bacterial small molecule. Science 321, 259–263.
Krediet, C.J., Ritchie, K.B., Paul, V.J., Teplitski, M., 2013. Coral-associated micro-organisms and their roles in promoting coral health and thwarting diseases. Proc. R. Soc. B Biol. Sci. 280, 20122328.
Kulik, E.M., Sandmeier, H., Hinni, K., Meyer, J., 2001. Identification of archaeal rDNA from subgingival dental plaque by PCR amplification and sequence analysis. FEMS Microbiol. Lett. 196, 129–133.
Kumar, S., Stecher, G., Tamura, K., 2016. MEGA7: molecular evolutionary genetics analysis version 7.0 for bigger datasets. Mol. Biol. Evol. 33, 1870–1874.
Kuwahara, H., Yoshida, T., Takaki, Y., Shimamura, S., Nishi, S., Harada, M., Matsuyama, K., Takishita, K., Kawato, M., Uematsu, K., Fujiwara, Y., Sato, T., Kato, C., Kitagawa, M., Kato, I., Marujama, T., 2007. Reduced genome of the thioautotrophic intracellular symbiont in a deep-sea clam, *Calyptogena okutanii*. Curr. Biol. 17, 881–886.
Lackner, G., Peters, E.E., Helfrich, E.J.N., Piel, J., 2017. Insights into the lifestyle of uncultured bacterial natural product factories associated with marine sponges. Proc. Natl. Acad. Sci. USA 114, E347–E356.
Landini, P., Antoniani, D., Burgess, J.G., Nijland, R., 2010. Molecular mechanisms of compounds affecting bacterial biofilm formation and dispersal. Appl. Microbiol. Biotechnol. 86, 813–823.
Laplace, P.S. de, 1796. Exposition du Systême du Monde. Cercle-Social, Paris.
Lederberg, J., McCray, A.T., 2001. 'Ome Sweet 'Omics — a genealogical treasury of words. Scientist 15, 8.
Lesser, M.P., Falcón, L.I., Rodríguez-Román, A., Enríquez, S., Hoegh-Guldberg, O., Iglesias-Prieto, R., 2007. Nitrogen fixation by symbiotic cyanobacteria provides a source of nitrogen for the scleractinian coral *Montastraea cavernosa*. Mar. Ecol. Prog. Ser. 346, 143–152.
Levis, N.A., Pfennig, D.W., 2016. Evaluating 'plasticity-first' evolution in nature: key criteria and empirical approaches. Trends Ecol. Evol. 31, 563–574.
Ley, R.E., Bäckhed, F., Turnbaugh, P., Lozupone, C.A., Knight, R.D., Gordon, J.I., 2005. Obesity alters gut microbial ecology. Proc. Natl. Acad. Sci. USA 102, 11070–11075.
Li, J., Li, J.-W., Feng, Z., Wang, J., An, H., Liu, Y., Wang, Y., Wang, K., Zhang, X., Miao, Z., Liang, W., Sebra, R., Wang, G., Wang, W.-C., Zhang, J.-R., 2016. Epigenetic switch driven by DNA inversions dictates phase variation in *Streptococcus pneumoniae*. PLoS Pathog. 12, e1005762.
Liew, Y.J., Li, Y., Baumgarten, S., Voolstra, C.R., Aranda, M., 2017. Condition-specific RNA editing in the coral symbiont *Symbiodinium microadriaticum*. PLoS Genet. 13, e1006619.
Lozupone, C.A., Stombaugh, J.I., Gordon, J.I., Jansson, J.K., Knight, R., 2012. Diversity, stability and resilience of the human gut microbiota. Nature 489, 220–230.
Lugtenberg, B., Kamilova, F., 2009. Plant-growth-promoting rhizobacteria. Annu. Rev. Microbiol. 63, 541–556.
Lynch, V.J., Nnamani, M.C., Kapusta, A., Brayer, K., Plaza, S.L., Mazur, E.C., Emera, D., Sheikh, S.Z., Grützner, F., Bauersachs, S., Graf, A., Young, S.L., Lieb, J.D., DeMayo, F.J., Feschotte, C., Wagner, G.P., 2015. Ancient transposable elements transformed the uterine regulatory landscape and transcriptome during the evolution of mammalian pregnancy. Cell Rep. 10, 551–561.
Margulis, L., 1981. Symbiosis in Cell Evolution. W.H. Freeman, New York.
Mathesius, U., Mulders, S., Gao, M., Teplitski, M., Caetano-Anollés, G., Rolfe, B.G., Bauer, W.D., 2003. Extensive and specific responses of a eukaryote to bacterial quorum-sensing signals. Proc. Natl. Acad. Sci. USA 100, 1444–1449.
Mayor, M., Queloz, D., 1995. A Jupiter-mass companion to a solar-type star. Nature 378, 355–359.
McFall-Ngai, M.J., 2002. Unseen forces: the influence of bacteria on animal development. Develop. Biol. 242, 1–14.
McFall-Ngai, M., 2007. Adaptive immunity: care for the community. Nature 445, 153.
McFall-Ngai, M., Hadfield, M.G., Bosch, T.C.G., Carey, H.V., Domazet-Lošo, T., Douglas, A.E., Dubilier, N., Eberl, G., Fukami, T., Gilbert, S.F., Hentschel, U., King, N., Kjelleberg, S., Knoll, A.H., Kremer, N., Mazmanian, S.K., Metcalf, J.L., Nealson, K., Pierce, N.E., Rawls, J.F., Reid, A., Ruby, E.G., Rumpho, M., Sanders, J.G., Tautz, D., Wernegreen, J.J., 2013. Animals in a bacterial world, a new imperative for the life sciences. Proc. Natl. Acad. Sci. USA 110, 3229–3236.
McMullin, E.R., Bergquist, D.C., Fisher, C.R., 2000. Metazoans in extreme environments: adaptations of hydrothermal vent and hydrocarbon seep fauna. Gravit. Space Biol. Bull. 13, 13–23.
Mies, M., Sumida, P.Y.G., Rädecker, N., Voolstra, C.R., 2017. Marine invertebrate larvae associated with *Symbiodinium*: a mutualism from the start? Front. Ecol. Evol. 5, 1–11.
Miller, C.B., Wheeler, P.A., 2012. Biological Oceanography, 2nd ed. Wiley-Blackwell, Chichester, UK.
Miller, T.L., Wolin, M.J., Conway de Macario, E., Macario, A.J., 1982. Isolation of *Methanobrevibacter smithii* from human feces. Appl. Environ. Microbiol. 43, 227–232.
Minic, Z., Hervé, G., 2004. Biochemical and enzymological aspects of the symbiosis between the deep-sea tubeworm *Riftia pachyptila* and its bacterial endosymbiont. FEBS J. 271, 3093–3102.
Moberg, F., Folke, C., 1999. Ecological goods and services of coral reef ecosystems. Ecol. Econ. 29, 215–233.
Moissl-Eichinger, C., Pausan, M., Taffner, J., Berg, G., Bang, C., Schmitz, R.A., 2017. Archaea are interactive components of complex microbiomes. Trends Microbiol. 26, 70–85.
Moitinho-Silva, L., Díez-Vives, C., Batani, G., Esteves, A.I., Jahn, M.T., Thomas, T., 2017a. Integrated metabolism in sponge–microbe symbiosis revealed by genome-centered metatranscriptomics. ISME J. 11, 1651–1666.
Moitinho-Silva, L., Steinert, G., Nielsen, S., Hardoim, C.C.P., Wu, Y.-C., McCormack, G.P., López-Legentil, S., Marchant, R., Webster, N., Thomas, T., Hentschel, U., 2017b. Predicting the HMA-LMA status in marine sponges by machine learning. Front. Microbiol. 8, 752.
Moran, N.A., 2002. Microbial minimalism: genome reduction in bacterial pathogens. Cell 108, 583–586.
Moran, N.A., Yun, Y., 2015. Experimental replacement of an obligate insect symbiont. Proc. Natl. Acad. Sci. USA 112, 2093–2096.
Moran, N.A., McCutcheon, J.P., Nakabachi, A., 2008. Genomics and evolution of heritable bacterial symbionts. Annu. Rev. Genet. 42, 165–190.
Mortzfeld, B.M., Urbanski, S., Reitzel, A.M., Künzel, S., Technau, U., Fraune, S., 2016. Response of bacterial colonization in *Nematostella vectensis* to development, environment and biogeography. Environ. Microbiol. 18, 1764–1781.
Muller, E.B., Kooijman, S.A.L.M., Edmunds, P.J., Doyle, F.J., Nisbet, R.M., 2009. Dynamic energy budgets in syntrophic symbiotic relationships between heterotrophic hosts and photoautotrophic symbionts. J. Theor. Biol. 259, 44–57.
Muscatine, L., Kaplan, I.R., 1994. Resource partitioning by reef corals as determined from stable isotope composition. Pacific Sci. 48, 304–312.
Muscatine, L., Neckelmann, N., 1981. Regulation of numbers of algae in the *Hydra–Chlorella* symbiosis. Ber. Dtsch. Bot. Ges. 94, 571–582.
Muscatine, L., Porter, J.W., 1977. Reef corals: mutualistic symbioses adapted to nutrient-poor environments. Bioscience 27, 454–460.
Muscatine, L., Cook, C., Pardy, R., Pool, R., 1975. Uptake, recognition and maintenance of symbiotic *Chlorella* by *Hydra viridis*. Symp. Soc. Exp. Biol. 29, 175–204.
Nakagawa, S., Takai, K., 2008. Deep-sea vent chemoautotrophs: diversity, biochemistry and ecological significance. EMS Microbiol. Ecol. 65, 1–14.
Nikoh, N., Nakabachi, A., 2009. Aphids acquired symbiotic genes via lateral gene transfer. BMC Biol. 7, 12.
Nursall, J.R., 1959. Oxygen as a prerequisite to the orgin of the Metazoa. Nature 183, 1170–1172.
Nussbaumer, A., Charles, R.F., Bright, M., 2006. Horizontal endosymbiont transmission in hydrothermal vent tubeworms. Nature 7091, 345–348.
Nys, R. d., Givskov, M., Kumar, N., Kjelleberg, S., Steinberg, P., 2006. Furanones. In: Fusetani, N., Clare, A.S. (Eds.), Antifouling Compounds. Springer, Berlin, pp. 55–86.
O'Hara, A.M., Shanahan, F., 2006. The gut flora as a forgotten organ. EMBO Rep. 7, 688–693.
Oliver, K.M., Degnan, P.H., Hunter, M.S., Moran, N.A., 2009. Bacteriophages encode factors required for protection in a symbiotic mutualism. Science 325, 992–994.
Oliver, T.A., Palumbi, S.R., 2010. Many corals host thermally resistant symbionts in high-temperature habitat. Coral Reefs 30, 241–250.
Oliver, T.A., Palumbi, S.R., 2011. Do fluctuating temperature environments elevate coral thermal tolerance? Coral Reefs 30, 429–440.
Pacheco, A.R., Sperandio, V., 2009. Inter-kingdom signaling: chemical language between bacteria and host. Curr. Opin. Microbiol. 12, 192–198.
Palumbi, S.R., Barshis, D.J., Traylor-Knowles, N., Bay, R.A., 2014. Mechanisms of reef coral resistance to future climate change. Science 344, 895–898.
Pearson, C., Rogers, A., Sheader, M., 2002. The genetic structure of the rare lagoonal sea anemone, *Nematostella vectensis* Stephenson (Cnidaria; Anthozoa) in the United Kingdom based on RAPD analysis. Mol. Ecol. 11, 2285–2293.
Petersen, J.M., Wentrup, C., Verna, C., Knitel, K., Dubilier, N., 2012. Origins and evolutionary flexibility of chemosynthetic symbionts from deep-sea animals. Biol. Bull. 223, 123–137.
Pietschke, C., Treitz, C., Forêt, S., Schultze, A., Künzel, S., Tholey, A., Bosch, T.C.G., Fraune, S., 2017. Host modification of a bacterial quorum sensing signal induces a

phenotypic switch in bacterial symbionts. Proc. Natl. Acad. Sci. USA 114, E8488–8497.
Pita, L., Fraune, S., Hentschel, U., 2016. Emerging sponge models of animal–microbe symbioses. Front. Microbiol. 7, 2102.
Pogoreutz, C., Rädecker, N., Cárdenas, A., Gärdes, A., Voolstra, C.R., Wild, C., 2017a. Sugar enrichment provides evidence for a role of nitrogen fixation in coral bleaching. Glob. Change Biol. 23, 3838–3848.
Pogoreutz, C., Rädecker, N., Cárdenas, A., Gärdes, A., Wild, C., Voolstra, C.R., 2017b. Nitrogen fixation aligns with nifH abundance and expression in two coral trophic functional groups. Front. Microbiol. 8, 1187.
Pogoreutz, C., Rädecker, N., Cárdenas, A., Gärdes, A., Wild, C., Voolstra, C.R., 2018. Dominance of *Endozoicomonas* bacteria throughout coral bleaching and mortality suggests structural inflexibility of the *Pocillopora verrucosa* microbiome. Ecol. Evol. 8 (4), 2240–2252. http://dx.doi.org/10.1002/ece3.3830.
Ponnudurai, R., Kleiner, M., Sayavedra, L., Petersen, J.M., Moche, M., Otto, A., Becher, D., Takeuchi, T., Satoh, N., Dubilier, N., Schweder, T., Markert, S., 2017. Metabolic and physiological interdependencies in the *Bathymodiolus azoricus* symbiosis. ISME J. 11, 463–477.
Pörtner, H., 2001. Climate change and temperature-dependent biogeography: oxygen limitation of thermal tolerance in animals. Naturwissenschaften 88, 137–146.
Probst, A.J., Auerbach, A.K., Moissl-Eichinger, C., 2013. Archaea on human skin. PLOS ONE 8, e65388.
Putnam, H.M., Barott, K.L., Ainsworth, T.D., Gates, R.D., 2017. The vulnerability and resilience of reef-building corals. Curr. Biol. 27, R528–R540.
Rädecker, N., Pogoreutz, C., Voolstra, C.R., Wiedenmann, J., Wild, C., 2015. Nitrogen cycling in corals: the key to understanding holobiont functioning? Trends Microbiol. 23, 490–497.
Rädecker, N., Raina, J.-B., Pernice, M., Perna, G., Guagliardo, P., Killburn, M., Aranda, M., Voolstra, C.R., 2017. *Aiptasia* as a model to study metabolic diversity and specificity in cnidarian–dinoflagellate symbioses. bioRxiv. http://dx.doi.org/10.1101/223933.
Raffaelli, D.G., Hawkins, S.J., 1999. Intertidal Ecology. Kluwer Academic Publishers/Springer Netherlands, Dordrecht.
Rahav, O., Dubinsky, Z., Achituv, Y., Falkowski, P.G., 1989. Ammonium metabolism in the zooxanthellate coral, *Stylophora pistillata*. Proc. R. Soc. B Biol. Sci. 236, 325–337.
Raina, J.B., Dinsdale, E.A., Willis, B.L., Bourne, D.G., 2010. Do the organic sulfur compounds DMSP and DMS drive coral microbial associations? Trends Microbiol. 18, 101–108.
Raina, J.-B., Tapiolas, D.M., Forêt, S., Lutz, A., Abrego, D., Ceh, J., Seneca, F.O., Clode, P.L., Bourne, D.G., Willis, B.L., Motti, C.A., 2013. DMSP biosynthesis by an animal and its role in coral thermal stress response. Nature 502, 677–680.
Raj, A., van Oudenaarden, A., 2008. Nature, nurture, or chance: stochastic gene expression and its consequences. Cell 135, 216–226.
Redman, R.S., Freeman, S., Clifton, D.R., Morrel, J., Brown, G., Rodriguez, R.J., 1999. Biochemical analysis of plant protection afforded by a nonpathogenic endophytic mutant of *Colletotrichum magna*. Plant Physiol. 119, 795–804.
Redman, R.S., Sheehan, K.B., Stout, R.G., Rodriguez, R.J., Henson, J.M., 2002. Thermotolerance conferred to plant host and fungal endophyte during mutualistic symbiosis. Science 298, 1581.
Reitzel, A., Darling, J., Sullivan, J., Finnerty, J., 2008. Global population genetic structure of the starlet anemone *Nematostella vectensis*: multiple introductions and implications for conservation policy. Biol. Invas. 10, 1197–1213.
Reitzel, A., Chu, T., Edquist, S., Genovese, C., Church, C., Tarrant, A., Finnerty, J.R., 2013a. Physiological and developmental responses to temperature by the sea anemone *Nematostella vectensis*. Mar. Ecol. Prog. Ser. 484, 115–130.
Reitzel, A.M., Herrera, S., Layden, M.J., Martindale, M.Q., Shank, T.M., 2013b. Going where traditional markers have not gone before: utility of and promise for RAD sequencing in marine invertebrate phylogeography and population genomics. Mol. Ecol. 22, 2953–2970.
Reshef, L., Koren, O., Loya, Y., Zilber-Rosenberg, I., Rosenberg, E., 2006. The coral probiotic hypothesis. Environ. Microbiol. 8, 2068–2073.
Rix, L., de Goeij, J.M., Mueller, C.E., Struck, U., Middelburg, J.J., van Duyl, F.C., Al-Horani, F.A., Wild, C., Naumann, M.S., van Oevelen, D., 2016. Coral mucus fuels the sponge loop in warm- and cold-water coral reef ecosystems. Sci. Rep. 6, 18715.
Rodriguez, R.J., Henson, J., Van Volkenburgh, E., Hoy, M., Wright, L., Beckwith, F., Kim, Y.O., Redman, R.S., 2008. Stress tolerance in plants via habitat-adapted symbiosis. ISME J. 2, 404–416.
Rohwer, F., Seguritan, V., Azam, F., Knowlton, N., 2002. Diversity and distribution of coral-associated bacteria. Mar. Ecol. Prog. Ser. 243, 1–10.
Rohwer, F., Youle, M., Vosten, D., 2010. Coral Reefs in the Microbial Seas. Plaid Press, Granada Hills, CA.
Rosenberg, E., Zilber-Rosenberg, I., 2016. Microbes drive evolution of animals and plants: the hologenome. MBio 7, e01395.
Rosenberg, E., Koren, O., Reshef, L., Efrony, R., Zilber-Rosenberg, I., 2007. The role of microorganisms in coral health, disease and evolution. Nat. Rev. Microbiol. 5, 355–362.
Ruby, E.G., 2008. Symbiotic conversations are revealed under genetic interrogation. Nat. Rev. Microbiol. 6, 752–762.
Russell, S.L., Corbett-Detig, R.B., Cavanaugh, C.M., 2017. Mixed transmission modes and dynamic genome evolution in an obligate animal–bacterial symbiosis. ISME J. 11, 1359–1371.
Sammarco, P.W., Risk, M.J., Schwarcz, H.P., Heikoop, J.M., 1999. Cross-continental shelf trends in coral δ15N on the Great Barrier Reef: further consideration of the reef nutrient paradox. Mar. Ecol. Prog. Ser. 180, 131–138.
Samuel, B.S., Gordon, J.I., 2006. A humanized gnotobiotic mouse model of host-archaeal-bacterial mutualism. Proc. Natl. Acad. Sci. USA 103, 10011–10016.
Samuel, B.S., Hansen, E.E., Manchester, J.K., Coutinho, P.M., Henrissat, P., Fulton, R., Latreille, P., Kim, K., Wilson, R.K., Gordon, J.I., 2007. Genomic and metabolic adaptations of *Methanobrevibacter smithii* to the human gut. Proc. Natl. Acad. Sci. USA 104, 10643–10648.
Sanchez-Contreras, M., Bauer, W.D., Gao, M., Robinson, J.B., Downie, J.A., 2007. Quorum-sensing regulation in rhizobia and its role in symbiotic interactions with legumes. Phil. Trans. R. Soc. Lond. B 362, 1149–1163.
Sanjuán, R., Nebot, M.R., Chirico, N., Mansky, L.M., Belshaw, R., 2010. Viral mutation rates. J. Virol. 84, 9733–9748.
Schoepf, V., Stat, M., Falter, J.L., McCulloch, M.T., 2015. Limits to the thermal tolerance of corals adapted to a highly fluctuating, naturally extreme temperature environment. Sci. Rep. 5, 17639.
Shantz, A.A., Lemoine, N.P., Burkepile, D.E., 2015. Nutrient loading alters the performance of key nutrient exchange mutualisms. Ecol. Lett. 19, 20–28.
Silverstein, R.N., Cunning, R., Baker, A.C., 2014. Change in algal symbiont communities after bleaching, not prior heat exposure, increases heat tolerance of reef corals. Glob. Chang. Biol. 21, 236–249.
Slaby, B.M., Hackl, T., Horn, H., Bayer, K., Hentschel, U., 2017. Metagenomic binning of a marine sponge microbiome reveals unity in defense but metabolic specialization. ISME J. 17, 2465–2478.
Smillie, C.S., Smith, M.B., Friedman, J., Cordero, O.X., David, L.A., Alm, E.J., 2011. Ecology drives a global network of gene exchange connecting the human microbiome. Nature 480, 241–244.
Soen, Y., 2014. Environmental disruption of host–microbe co-adaptation as a potential driving force in evolution. Front. Genet. 5, 168.
Spang, A., Saw, H.J., Jorgensen, S.L., Zaremba-Niedzwiedzka, K., Martin, J., Lind, A.E., van Eijk, R., Schleper, C., Guy, L., Ettema, T.J.G., 2015. Complex archaea that bridge the gap between prokaryotes and eukaryotes. Nature 521, 173–179.
Sperandio, V., Torres, A.G., Jarvis, B., Nataro, J.P., Kaper, J.B., 2003. Bacteria–host communication: the language of hormones. Proc. Natl. Acad. Sci. USA 100, 8951–8956.
Stein, E., Molitor, A., Kogel, K.H., Waller, F., 2008. Systemic resistance in *Arabidopsis* conferred by the mycorrhizal fungus *Piriformospora indica* requires jasmonic acid signaling and the cytoplasmic function of NPR1. Plant Cell Physiol. 49, 1747–1751.
Sullivan, J.C., Wolenski, F.S., Reitzel, A.M., French, C.E., Traylor-Knowles, N., Gilmore, T.D., Finnerty, J.R., 2009. Two alleles of NF-kappaB in the sea anemone *Nematostella vectensis* are widely dispersed in nature and encode proteins with distinct activities. PLoS One 4, e7311.
Sundquist, A., Bigdeli, S., Jalili, R., Druzin, M.L., Waller, S., Pullen, K.M., El-Sayed, Y.Y., Taslimi, M.M., Batzoglou, S., Ronaghi, M., 2007. Bacterial flora-typing with targeted, chip-based pyrosequencing. BMC Microbiol. 7, 108.
Suttle, C.A., 2005. Viruses in the sea. Nature 437, 356–361.
Suttle, C.A., 2016. Environmental microbiology: viral diversity on the global stage. Nature Microbiol. 1, 16205.
Suzuki, Y., Sasaki, T., Suzuki, M., Nogi, Y., Miwa, T., Takai, K., Nealson, K.H., Horikoshi, K., 2005. Novel chemoautotrophic endosymbiosis between a member of the Epsilonproteobacteria and the hydrothermal-vent gastropod *Alviniconcha* aff. *hessleri* (Gastropoda: Provannidae) from the Indian Ocean. Appl. Environ. Microbiol. 71, 5440–5450.
Swedenborg, E., 1734. Principia rerum naturalium. Hekel, Dresden.
Sweet, M.J., Brown, B.E., Dunne, R.P., Singleton, I., Bulling, M., 2017. Evidence for rapid, tide-related shifts in the microbiome of the coral *Coelastrea aspera*. Coral Reefs 36, 815–828.
Tanaka, Y., Suzuki, A., Sakai, K., 2018. The stoichiometry of coral–dinoflagellate symbiosis: carbon and nitrogen cycles are balanced in the recycling and double translocation system. ISME J.(Jan). http://dx.doi.org/10.1038/s41396-017-0019-3. Epub ahead of print.
Telford, G., Wheeler, D., Williams, P., Tomkins, P.T., Appleby, P., Sewell, H., Stewart, G.S., Bycroft, B.W., Pritchard, D.I., 1998. The *Pseudomonas aeruginosa* quorum-sensing signal molecule *N*-(3-oxododecanoyl)-L-homoserine lactone has immunomodulatory activity. Infect Immun. 66, 36–42.
Thauer, R.K., Shima, S., 2006. Biogeochemistry: methane and microbes. Nature 440, 878–879.
Theis, K.R., Dheilly, N.M., Klassen, J.L., Brucker, R.M., John, F., Bosch, T.C.G., Cryan, J.F., Gilbert, S.F., Goodnight, C.J., Lloyd, E.A., Sapp, J., Vandenkoornhuyse, P., Rosenberg, I.Z., 2016. Getting the hologenome concept right: an eco-evolutionary framework for hosts and their microbiomes. mSystems 1 e00028-16.
Thomas, T., Rusch, D., DeMaere, M.Z., Yung, P.Y., Lewis, M., Halpern, A., Heidelberg, K.B., Egan, S., Steinberg, P.D., Kjelleberg, S., 2010. Functional genomic signatures of sponge bacteria reveal unique and shared features of symbiosis. ISME J. 4, 1557–1567.
Thomas, T., Moitinho-Silva, L., Lurgi, M., Björk, J.R., Easson, C., Astudillo, C., Olson, J.B., Erwin, P.M., López-Legentil, S., Luter, H., Chaves-Fonnegra, A., Costa, R., Schupp, P., Steindler, L., Erpenbeck, D., Gilbert, J., Knight, R., Ackerman, G., Lopez, J.V., Taylor, M.W., Thacker, R.W., Montoya, J.M., Hentschel, U., Webster, N., 2016. Global sponge microbiome: diversity, structure and convergent evolution of symbiont communities across the phylum Porifera. Nature Comm. 7, 11870.
Torda, G., Donelson, J.M., Aranda, M., Barshis, D.J., Bay, L., Berumen, M.L., Bourne, D.G., Cantin, N., Foret, S., Matz, M., Miller, D.J., Moya, A., Putnam, H.M., Ravasi, T., van Oppen, M.J.H., Vega Thurber, R., Vidal-Dupiol, J., Voolstra, C.R., Watson, S.-A., Whitelaw, E., Willis, B.L., Munday, P.L., 2017. Rapid adaptive responses to climate change in corals. Nat. Clim. Change 7, 627–637.
Toruño, T.Y., Stergiopoulos, I., Coaker, G., 2016. Plant–pathogen effectors: cellular probes interfering with plant defenses in spatial and temporal manners. Annu. Rev. Phytopathol. 54, 419–441.
Travis, J.M.J., Travis, E.R., 2002. Mutator dynamics in fluctuating environments. Proc. R.

Soc. Lond. B 269, 591–597.
Tremaroli, V., Bäckhed, F., 2012. Functional interactions between the gut microbiota and host metabolism. Nature 489, 242–249.
Tremblay, P., Grover, R., Maguer, J.F., Legendre, L., Ferrier-Pagès, C., 2012. Autotrophic carbon budget in coral tissue: a new 13C-based model of photosynthate translocation. J. Exp. Biol. 215, 1384–1393.
Triantafyllou, K., Chang, C., Pimentel, M., 2014. Methanogens, methane and gastrointestinal motility. J. Neurogastroenterol. Motil. 20, 31–40.
Tsuchida, T., Koga, R., Horikawa, M., Tsunoda, T., Maoka, T., Matsumoto, S., Simon, J.C., Fukatsu, T., 2010. Symbiotic bacterium modifies aphid body color. Science 330, 1102–1104.
Ueda, K., Kawabata, R., Irie, T., Nakai, Y., Tohya, Y., Sakaguchi, T., 2013. Inactivation of pathogenic viruses by plant-derived tannins: strong effects of extracts from persimmon (*Diospyros kaki*) on a broad range of viruses. PLoS One 8, e55343.
Valentine, D.L., 2007. Adaptations to energy stress dictate the ecology and evolution of the Archaea. Nature Rev. Microbiol. 5, 316–323.
Van der Woude, M.W., 2011. Phase variation: how to create and coordinate population diversity. Curr. Opin. Microbiol. 14, 205–211.
Van Dover, C.L., 2000. The Ecology of Deep-Sea Hydrothermal Vents. Princeton University Press, Princeton.
Van Hulten, M., Pelser, M., Van Loon, L.C., Pieterse, C.M.J., Ton, J., 2006. Costs and benefits of priming for defense in *Arabidopsis*. Proc. Natl. Acad. Sci. USA 103, 5602–5607.
Van Loon, L.C., 2007. Plant responses to plant growth-promoting rhizobacteria. European J. Plant Pathol. 119, 243–254.
Vianna, M.E., Conrads, G., Gomes, B.P.F.A., Horz, H.P., 2006. Identification and quantification of archaea involved in primary endodontic infections. J. Clin. Microbiol. 44, 1274–1282.
Vianna, M.E., Holtgraewe, S., Seyfarth, I., Conrads, G., Horz, H.P., 2008. Quantitative analysis of three hydrogenotrophic microbial groups, methanogenic archaea, sulfate-reducing bacteria, and acetogenic bacteria, within plaque biofilms associated with human periodontal disease. J. Bacteriol. 190, 3779–3785.
Vierbuchen, T., Bang, C., Rosigkeit, H., Schmitz, R.A., Heine, H., 2017. The human-associated archaeon *Methanosphaera stadtmanae* is recognized through its RNA and induces TLR8-dependent NLRP3 inflammasome activation. Front. Immunol. 8, 1535.
Virgilio, M., Backeljau, T., Abbiati, M., 2006. Mitochondrial DNA and allozyme patterns of *Hediste diversicolor* (Polychaeta: Nereididae): the importance of small scale genetic structuring. Mar. Ecol. Prog. Ser. 326, 157–165.
Vitousek, P.M., Howarth, R.W., 1991. Nitrogen limitation on land and in the sea: how can it occur? Biogeochemistry 13, 87–115.
Voolstra, C.R., Miller, D.J., Ragan, M.A., Hoffmann, A., Hoegh-, O., Bourne, D., Ball, E., Ying, H., Foret, S., Takahashi, S., Weynberg, K.D., Oppen, M.J., Van Morrow, K., Chan, C.X., Leggat, W., Sprungala, S., Imelfort, M., Tyson, G.W., Lundgren, P., Beeden, R., Ravasi, T., Berumen, M., 2015. The ReFuGe 2020 Consortium – using "omics" approaches to explore the adaptability and resilience of coral holobionts to environmental change. Front. Mar. Sci. 2, 68.
Waidele, L., Korb, J., Voolstra, C.R., Künzel, S., Dedeine, F., Staubach, F., 2017. Differential ecological specificity of protist and bacterial microbiomes across a set of termite species. Front. Microbiol. 8, 2518.
Waldor, M.K., Tyson, G., Borenstein, E., Ochman, H., Moeller, A., Finlay, B.B., Kong, H.H., Gordon, J.I., Nelson, K.E., Dabbag, K., Smith, H., 2015. Where next for microbiome research? PLoS Biol. 13 e1002050.
Waller, F., Achatz, B., Baltruschat, H., Fodor, J., Becker, K., Fischer, M., Heier, T., Hückelhoven, R., Neumann, C., von Wettstein, D., Franken, P., Kogel, K.H., 2005. The endophytic fungus *Piriformospora indica* reprograms barley to salt-stress tolerance, disease resistance, and higher yield. Proc. Natl. Acad. Sci. USA 102, 13386–13391.
Ward, D., 2016. The Biology of Deserts. Biology of Habitats Series, 2nd ed. Oxford University Press, Oxford.
Weber, A.P.M., Horst, R.J., Barbier, G.G., Oesterhelt, C., 2007. Metabolism and metabolomics of eukaryotes living under extreme conditions. Int. Rev. Cytol. 256, 1–34.
Webster, N.S., Reusch, T.B.H., 2017. Microbial contributions to the persistence of coral reefs. ISME J. 11, 2167–2174.
Webster, N.S., Thomas, T., 2016. The sponge hologenome. MBio 7, e00135–16.
Wegley, L., Edwards, R., Rodriguez-Brito, B., Liu, H., Rohwer, F., 2007. Metagenomic analysis of the microbial community associated with the coral *Porites astreoides*. Environ. Microbiol. 9, 2707–2719.
Weiland-Bräuer, N., Schmitz, R.A., 2017. Quenching bacterial communication: innovative strategies for biofilm inhibition. In: Méndez-Vilas, A. (Ed.), Antimicrobial Research: Novel Bioknowledge and Educational Programs. Formatex Research Center, Badajoz, pp. 331–343.
Weiland-Bräuer, N., Pinnow, N., Schmitz, R.A., 2015. Novel reporter for identification of interference with acyl homoserine lactone and autoinducer-2 quorum sensing. Appl. Environ. Microbiol. 81, 1477–1489.
Wentrup, C., Wendeberg, A., Schimak, M., Borowski, C., Dubilier, N., 2014. Forever competent: deep-sea bivalves are colonized by their chemosynthetic symbionts throughout their lifetime. Environ. Microbiol. 16, 3699–3713.
Wetz, K., Kucinski, T., 1991. Influence of different ionic and pH environments on structural alterations of poliovirus and their possible relation to virus uncoating. J. Gen. Virol. 72, 2541–2544.
Wild, C., Rasheed, M., Werner, U., Franke, U., Johnstone, R., Huettel, M., 2004a. Degradation and mineralization of coral mucus in reef environments. Mar. Ecol. Prog. Ser. 267, 159–171.
Wild, C., Huettel, M., Klueter, A., Kremb, S.G., Rasheed, M.Y.M., Jørgensen, B.B., 2004b. Coral mucus functions as an energy carrier and particle trap in the reef ecosystem. Nature 428, 66–70.
Wilkinson, C.R., Fay, P., 1979. Nitrogen fixation in coral reef sponges with symbiotic cyanobacteria. Nature 279, 527–529.
Wittebolle, L., Marzorati, M., Clement, L., Balloi, A., Daffonchio, D., Heylen, K., De Vos, P., Verstraete, W., Boon, N., 2009. Initial community evenness favours functionality under selective stress. Nature 458, 623–626.
Woese, C.R., 1987. Bacterial evolution. Microbiol. Rev. 51, 221–271.
Woese, C.R., Fox, G.E., 1977. Phylogenetic structure of the prokaryotic domain: the primary kingdoms. Proc. Natl. Acad. Sci. USA 74, 5088–5090.
Woese, C.R., Kandler, O., Wheelis, M.L., 1990. Towards a natural system of organisms: proposal for the domains Archaea, Bacteria, and Eucarya. Proc. Natl. Acad. Sci. USA 87, 4576–4579.
Wooldridge, S.A., 2013. Breakdown of the coral–algae symbiosis: towards formalising a linkage between warm-water bleaching thresholds and the growth rate of the intracellular zooxanthellae. Biogeosciences 10, 1647–1658.
Yamabe, K., Maeda, H., Kokeguchi, S., Tanimoto, I., Sonoi, N., Asakawa, S., Takashiba, S., 2008. Distribution of Archaea in Japanese patients with periodontitis and humoral immune response to the components. FEMS Microbiol. Lett. 287, 69–75.
Yellowlees, D., Rees, T.A.V., Leggat, W., 2008. Metabolic interactions between algal symbionts and invertebrate hosts. Plant Cell Environ. 31, 679–694.
Zaborina, O., Lepine, F., Xiao, G., Valuckaite, V., Chen, Y., Li, T., Ciancio, M., Zaborin, A., Petroff, E., Turner, J.R., 2007. Dynorphin activates quorum sensing quinolone signaling in *Pseudomonas aeruginosa*. PLoS Pathog. 3, e35.
Zamioudis, C., Pieterse, C.M.J., 2012. Modulation of host immunity by beneficial microbes. Mol. Plant Microbe Interact. 25, 139–150.
Ziegler, M., FitzPatrick, S.K., Burghardt, I., Liberatoire, K.K., Leffler, A.J., Takacs-Vesbach, C., Shepherd, U., 2014. Thermal stress response in a dinoflagellate-bearing nudibranch and the octocoral on which it feeds. Coral Reefs 33, 1085–1099.
Ziegler, M., Roder, C., Büchel, C., Voolstra, C.R., 2015. Niche acclimatization in Red Sea corals is dependent on flexibility of host–symbiont association. Mar. Ecol. Prog. Ser. 533, 149–161.
Ziegler, M., Roik, A., Porter, A., Zubier, K., Mudarris, M.S., Ormond, R., Voolstra, C.R., 2016. Coral microbial community dynamics in response to anthropogenic impacts near a major city in the central Red Sea. Mar. Poll. Bull. 105, 629–640.
Ziegler, M., Seneca, F.O., Yum, L.K., Palumbi, S.R., Voolstra, C.R., 2017. Bacterial community dynamics are linked to patterns of coral heat tolerance. Nat. Commun. 8, 14213.
Zilber-Rosenberg, I., Rosenberg, E., 2008. Role of microorganisms in the evolution of animals and plants: the hologenome theory of evolution. FEMS Microbiol. Lett. 32, 723–735.
Zuo, G., Xu, Z., Hao, B., 2015. Phylogeny and taxonomy of Archaea: a comparison of the whole-genome-based CVTree approach with 16S rRNA sequence analysis. Life 5, 949–968.