1 **Symbiodiniaceae-bacteria interactions: rethinking metabolite exchange in**

2 **reef-building corals as multi-partner metabolic networks.**

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4 **Running Title: Corals as multi-partner metabolic networks.**

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17 **Summary**

18 The intimate relationship between scleractinian corals and their associated microorganisms is

19 fundamental to healthy coral reef ecosystems. Coral-associated microbes (Symbiodiniaceae

20 and other protists, bacteria, archaea, fungi, and viruses) support coral health and resilience

21 through metabolite transfer, inter-partner signalling, and genetic exchange. However, much

22 of our understanding of the coral holobiont relationship has come from studies that have

23 investigated either coral-Symbiodiniaceae or coral-bacteria interactions in isolation, while

24 relatively little research has focused on other ecological and metabolic interactions

25 potentially occurring within the coral multi-partner symbiotic network. Recent evidences of

26 intimate coupling between phytoplankton and bacteria have demonstrated that obligate

27 resource exchange between partners fundamentally drives their ecological success. Here, we

28 posit that similar associations with bacterial consortia regulate Symbiodiniaceae productivity

29 and are in turn central to the health of corals. Indeed, we propose that this bacteria-

30 Symbiodiniaceae-coral relationship underpins the coral holobiont's nutrition, stress tolerance,

31 and potentially influences the future survival of coral reef ecosystems under changing

32 environmental conditions. Resolving Symbiodiniaceae-bacteria associations is therefore a

33 logical next step towards understanding the complex multi-partner interactions occurring in

34 the coral holobiont.

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36 **Keywords**: Symbiodiniaceae; microbiome; bacteria; coral; metabolism; symbiotic

37 interactions

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39 **Originality-Significance Statement**

40 Complex interspecific interactions between coral hosts and the multitude of symbiotic

41 microorganisms they harbour underpins the health and survival of coral reefs. However,

42 research to date has focused on coral host-unicellular algae (Symbiodiniaceae) or coral host–

43 prokaryote interactions, while other relationships within the coral holobiont have been

44 relatively overlooked. We propose to view the coral holobiont as a multi-partner metabolic

45 network, providing a paradigm shift from a bipartite symbiosis to a community-based

46 integration of factors that determine the resilience of coral reef organisms. We review

47 emerging evidence of the importance of the ecological relationships occurring between

48 marine phytoplankton and bacteria, and review Symbiodiniaceae-bacteria interactions that

49 could underpin Symbiodiniaceae ecological success and contribute to coral holobiont fitness.

50 Understanding these interactions is of critical importance for predicting the resilience and

51 adaptability of coral reefs to environmental change.

52

Introduction

Reef-building corals are holobionts, comprising the cnidarian host and its associated

microbes: dinoflagellates [Symbiodiniaceae, (LaJeunesse et al., 2018)] and other protists,

bacteria, archaea, fungi, and viruses (Rohwer et al., 2002; Kwong et al., 2019; Pernice et al.,

2019). The cnidarian host relies on the resources from these numerous symbionts to support

its energy budget, growth rate, fecundity and metabolism (Peixoto et al., 2017; Torda et al.,

2017). Indeed, coral-microorganism interactions have influenced the genomic evolution of

both the host and microorganism partners, shaped coral development, and defined the

ecological success of the coral holobiont (Thompson et al., 2015). Yet, of the multiple

potential interactions within the coral holobiont, research has generally focused on the coral-

dinoflagellate and coral-bacteria interactions e.g. (Webster et al., 2016; Hillyer et al., 2018),

and relatively few studies have investigated other potential inter-partner interactions (Fig. 1;

but see Table 1).

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Numerous studies have demonstrated that both endosymbiotic Symbiodiniaceae and

associated bacteria support the persistence of corals through the exchange of metabolites and

bioactive compounds (Rohwer et al., 2002; Cantin et al., 2009; Ainsworth et al., 2010;

Bourne et al., 2013; Glasl et al., 2016; Peixoto et al., 2017; Hillyer et al., 2018; Matthews et

al., 2018). Yet, remarkably, the role of bacteria in regulating Symbiodiniaceae resource

acquisition, competitive performance, and functional diversity (as both free-living and

endosymbionts) is relatively unexplored (Ritchie, 2012; Bourne et al., 2013; Ainsworth et al.,

2015; Peixoto et al., 2017; Silveira et al., 2017; Bernasconi et al., 2018); Table 1). This

fundamental gap in knowledge wholly constrains our understanding of how microbes act in

concert to regulate the health of coral holobionts, especially given the importance of

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bacterial-algal interactions for nutrient cycling, signal transduction and gene transfer as demonstrated for other microalgal taxa (Seymour et al., 2017). Emerging evidence suggests that interactions with bacterial associates may be important for Symbiodiniaceae nutrition and survival in their free-living state (Jeong et al., 2012; Frommlet et al., 2015; Lawson et al., 2018). Furthermore, global co-occurrence of specific bacterial taxa and Symbiodiniaceae in corals (Bernasconi et al., 2018) and co-localisation of distinct bacterial taxa with Symbiodiniaceae in cnidarian host tissues (Ainsworth et al., 2015) suggest specific Symbiodiniaceae-bacterial interactions may be crucial to support holobiont metabolic functioning. Exploring Symbiodiniaceae-bacteria associations is therefore a logical next step towards fully understanding the complex symbiotic interactions occurring in the coral holobiont, and assists development of conservation strategies for reefs under global climate change (van Oppen and Blackall, 2019).

Unlocking the significance of these interactions in Symbiodiniaceae ecological success could help answer fundamental questions surrounding coral reef function and resilience, including: 1) do obligate associations with bacterial symbionts enable Symbiodiniaceae to thrive as both free-living cells and endosymbionts?; 2) do interactions with bacteria promote the immense functional diversity observed for Symbiodiniaceae?; and 3) what role, if any, could Symbiodiniaceae-bacterial interactions play in the ecological success of the coral holobiont? Here, we consider that Symbiodiniaceae may hold an innate dependency on specific bacteria for resource exchange, thus forming an intimate association that may support optimum metabolic fitness of the coral holobiont. We present the current data supporting these relationships in the coral symbiotic network and explore how evidence from other algal-bacterial systems suggest Symbiodiniaceae-bacteria interactions may be a hidden key in determining the overall health and resilience of the coral holobiont.

Are bacteria obligate symbionts and "resource surrogates" for free-living

Symbiodiniaceae?

Metabolic exchange between autotrophic organisms and bacteria underpin the ecological

success of many plant and algal species across marine and terrestrial systems (Ramanan et al.,

2016). Bacterial and archaeal associates protect many eukaryotic hosts against pathogens,

supply and recycle essential nutrients (Ramanan et al., 2016), and even contribute to the

acclimatisation and adaptation of their host to environmental change (Schönknecht et al.,

2013). Phytoplankton-bacteria interactions drive the major oceanic biogeochemical cycles,

contribute to energy transfers to higher trophic levels, and to the emission of climate-

regulating gasses (Seymour et al., 2017). More specifically, bacteria can enhance the growth

of dinoflagellates through specific nutrient exchange (Croft et al., 2005), while dinoflagellate-

bacteria interactions may play a role in algal toxin production, e.g. neurotoxin production by

Alexandrium tamarense (Zhang et al., 2015). Furthermore, specific bacterial taxa are

consistently present in dinoflagellate cultures, including Symbiodiniaceae (Frommlet et al.,

2015; Lawson et al., 2018), which strongly suggests that associated bacteria carry out

important functions for these microalgae (Zhang et al., 2015).

The functional diversity of Symbiodiniaceae in terms of stress tolerance provides corals with

the capacity to respond to environmental change, and thus acquiring new Symbiodiniaceae

species from the environment or undergoing changes in the relative abundance of species

already present in the coral tissues can enable corals to acclimatise to increasing

environmental threats (Baker, 2003; Berkelmans and Van Oppen, 2006; Loram et al., 2007;

Stat and Gates, 2011; Boulotte et al., 2016; Hume et al., 2016). Recent evidence has

demonstrated the uptake of exogenous, thermally tolerant Symbiodiniaceae species by corals

in response to repeated temperature stress (Boulotte et al., 2016). Furthermore, molecular

125   studies have now confirmed that most Symbiodiniaceae genetic variants forming symbioses

126   spend part of their life-cycle as free living cells before colonising new coral recruits (Cunning

127   et al., 2015). Yet despite over 50 years of research examining Symbiodiniaceae biology and

128   ecology, relatively little is known about the free-living life stage of Symbiodiniaceae (Stat et

129   al., 2006; Takabayashi et al., 2012; Cunning et al., 2015; Suggett et al., 2017; LaJeunesse et

130   al., 2018). For instance, it is still unclear how Symbiodiniaceae thrive outside of the coral

131   tissues in oligotrophic waters and sediments without the concomitant provision of essential

132   nutrients.

133   Cultured Symbiodiniaceae predate on bacteria under both nutrient-replete and -depleted

134   conditions, demonstrating that heterotrophic feeding may be a survival strategy for

135   Symbiodiniaceae cells when free-living (Jeong et al., 2012). However, dependency upon

136   bacteria for resource acquisition by free-living Symbiodiniaceae likely extends far beyond

137   predation, and may also involve exchange of key metabolites (Seymour et al., 2017). For

138   example, *Sulfitobacter* species promote diatom growth through the secretion of indole-3-

139   acetic acid synthesised from diatom-derived tryptophan, demonstrating how mutual

140   exchanges of metabolites can influence the success of bacterial and phytoplankton partners

141   (Amin et al., 2015). Evidence for algal acquisition of vitamins (e.g. vitamin B12; (Croft et al.,

142   2005)), and enhanced micronutrient bioavailability (e.g. Fe (Amin et al., 2015), Zn (Ferrier-

143   Pagès et al., 2005)) through symbiotic relationships with specific bacteria further highlights

144   the important nutritional links between these groups of aquatic microorganisms.

145   Most dinoflagellates are difficult to grow axenically, which suggests that associated bacteria

146   provide necessary metabolic resources for successful dinoflagellate growth outside of the

147   host, and that these bacterial partners might operate as "resource surrogates" (Ritchie, 2012;

148   Suggett et al., 2017). Indeed, changes in bacterial community composition modify the growth

149   of the dinoflagellate *Gymnodinium catenatum* by approximately four-fold, which is

150   equivalent to growth enhancements triggered by a 5°C difference in temperature or a six-fold

151   difference in light intensity under laboratory conditions (Bolch et al., 2017). A recent study

152   confirmed that bacteria are abundant and diverse within most Symbiodiniaceae laboratory

153   cultures, and that some bacterial taxa are conserved across Symbiodiniaceae genera (Lawson

154   et al., 2018). Notably, members of the Rhodobacterales, a family of α-proteobacteria

155   commonly associated with many phytoplankton taxa, have been found in Symbiodiniaceae

156   cultures all over the world, suggesting these bacteria are conserved mutualists of

157   Symbiodiniaceae (Ritchie, 2012; Lawson et al., 2018). In culture, Symbiodiniaceae spp. and

158   associated bacteria form calcifying structures known as symbiolites (i.e. aragonitic

159   microbialites in which Symbiodiniaceae are encased) (Frommlet et al., 2015). Evidence

160   suggests symbiolite formation is a photosynthesis-induced bacterial-Symbiodiniaceae

161   calcification, which likely occurs in reef sediments as well (Frommlet et al., 2018). This is

162   the first evidence of metabolic coupling between Symbiodiniaceae and associated bacteria,

163   and identify an entirely new endolithic niche for free-living (benthic) Symbiodiniaceae. The

164   formation of symbiolites is likely ecologically important, as it can protect Symbiodiniaceae

165   from grazers and UV radiation, while still permitting photosynthesis (Friedmann, 1982;

166   Shashar et al., 1997; Jeong et al., 2012; Frommlet et al., 2018). These novel insights into

167   bacterial-Symbiodiniaceae associations reinforce how this coupling may be essential to the

168   fitness and life-cycle viability of the dinoflagellates, and may ultimately influence their

169   availability to new coral recruits. However there is as yet very little understanding of the

170   metabolic exchange between Symbiodiniaceae and their bacterial partners in the water

171   column, sediments and in endosymbiosis (Fig. 3).

172   Genome reduction and the exchange of metabolic intermediates between hosts and symbionts

173   are common phenomena of obligate symbioses, and the absence of important metabolic

174 pathways within an organism can point towards dependencies of symbiotic partners. For

175 example, the abundant coral genus *Acropora* lacks the enzyme responsible for cysteine

176 biosynthesis, implying this coral is dependent on its microbial symbionts for provision of this

177 amino acid (Shinzato et al., 2011). While still large compared to other microalgae, as a result

178 of idiosyncratic features such as multiple gene copies, Symbiodiniaceae genomes are small

179 relative to other dinoflagellates (Fig. S1), suggesting this family could have also lost

180 necessary components, such as key enzymes, due to obligate interactions with bacterial

181 symbionts, coral hosts, or other symbionts. Symbiodiniaceae-associated bacteria may provide

182 metabolic capabilities that are missing in the Symbiodiniaceae genome. Examples of

183 potential obligate bacterial contributions observed in other microalgae-bacteria interactions

184 include the ability to degrade complex polysaccharides, to reduce competition (Ramanan et

185 al., 2016) or to acquire bioavailable iron (Hopkinson and Morel, 2009)). Iron is essential for a

186 range of physiological processes in microalgae, including photosynthesis, respiration and

187 nitrogen fixation (Behrenfeld et al., 2009). Although, Symbiodiniaceae in a free-living state

188 can acquire bioavailable trace metals from ambient seawater using specific transporters

189 (Morel and Price, 2003), the concentrations of bioavailable iron in much of the global ocean

190 are too low to support microalgal growth (Hopkinson and Morel, 2009). Recent culturing

191 work examining trace metal availability demonstrated that the free-living *Fugacium*

192 *kawagutii* (previously *Symbiodinium kawagutii*) requires high concentrations of bioavailable

193 iron to achieve optimum growth (Rodriguez and Ho, 2018). Marine bacteria produce

194 siderophores, which bind and concentrate iron into bioavailable forms, enabling the uptake of

195 this limiting micronutrient by phytoplankton; for example, the production of siderophores by

196 the γ-proteobacterium *Marinobacter* promotes the growth of its dinoflagellate partner,

197 *Scrippsiella trochoidea* (Amin et al. 2009). Intriguingly, *Marinobacter* was also part of the

198 "core" bacterial-associates shared between diverse Symbiodiniaceae cultures (Lawson et al.,

199 2018). It is therefore likely that Symbiodiniaceae depend on bacterial associates to fulfil their

200 needs for bioavailable iron (Fig. 2).

201 Another important micronutrient is Vitamin B_{12} (cobalamin), a cofactor involved in the

202 production of the amino acid methionine, which is needed to synthesize every protein as well

203 as in diverse metabolic pathways including the generation of antioxidants glutathione and

204 DMSP (Croft et al., 2005). Cobalamin is synthesised by many heterotrophic bacteria and

205 nearly all oxygenic photosynthetic cyanobacteria but as with many algal protists,

206 Symbiodiniaceae require exogenous cobalamin for growth as they do not possess the genetic

207 machinery to generate the active form of this vitamin (Supplemental Information S1).

208 Genomic evidence suggests Symbiodiniaceae possess cobalamin-dependent methionine

209 synthase and not cobalamin-independent methionine synthase (Supplemental Information

210 S1), implying that free-living Symbiodiniaceae depend on bacterial symbionts to gain access

211 to this important cofactor.

212 **Do bacteria drive Symbiodiniaceae functional diversity?**

213 Substantial genetic and functional diversity of Symbiodiniaceae provides capacity for the

214 coral holobiont to respond to a broad range of environmental conditions (Sampayo et al.,

215 2009; Pettay et al., 2015; Boulotte et al., 2016; Hume et al., 2016; Silverstein et al., 2017;

216 Suggett et al., 2017; LaJeunesse et al., 2018), which is of immense ecological importance to

217 the survival and growth of coral reefs. There is high genetic divergence between

218 Symbiodiniaceae species (even those in the same genus) (Liu et al., 2018; González-Pech et

219 al., 2019); however, many of the drivers of the large functional diversity of Symbiodiniaceae

220 remain largely unresolved. Gene duplication and horizontal gene transfer are two drivers of

221 genome evolution, which promote the emergence of novel traits. Long-term symbiosis can

222 lead to the sharing of genetic traits between algae and their associated microbiome, which has

223   been proposed to have had a major impact on the gene content of algae (Keeling, 2009;

224   Schönknecht et al., 2014; Husnik and McCutcheon, 2018). For example, emerging genomic

225   evidence has shown that horizontal gene transfer from bacteria and archaea facilitates the

226   survival of the extremophilic, unicellular red alga, *Galdieria sulphuraria,* which lives in hot,

227   metal-rich, toxic and acidic environments (Schönknecht et al., 2013). A growing body of

228   evidence indicates that horizontal gene transfer is an important source of gene innovation in

229   dinoflagellates (Wisecaver et al., 2013). Gene transfer from associated bacteria may therefore

230   provide a similar adaptive mechanism for Symbiodiniaceae and may explain the large

231   functional diversity evident across the Symbiodiniaceae family. For example, members of the

232   Rhodobacterales, which have been found in close association with corals (Apprill, 2017) and

233   are an important component of the Symbiodiniaceae bacterial-associates (Lawson et al.,

234   2018), have a large propensity for transferring genes to other microbes in the marine

235   environment (McDaniel et al., 2010; Webster and Reusch, 2017). It is therefore plausible that

236   Symbiodiniaceae could acquire foreign genes from associated bacteria via bacteriophages or

237   similar genetic elements such as gene transfer agents (Solioz and Marrs, 1977; Shumaker et

238   al., 2019). Furthermore, microbes in coral reef environments show a much higher rate of

239   novel-trait acquisition by horizontal gene transfer than by spontaneous mutation, suggesting

240   an alternate mode of adaptation via swapping of potentially beneficial genes between marine

241   microbes (McDaniel et al., 2010), and possibly Symbiodiniaceae.

242   Horizontal symbiont acquisition, where offspring acquire symbionts from the environment,

243   could provide an opportunity for free-living Symbiodiniaceae and/or bacterial communities to

244   establish novel, potentially advantageous, associations with a cnidarian host. This mode of

245   Symbiodiniaceae transmission is observed in the majority of coral species and could allow

246   offspring to select a symbiont community that confers advantages locally. The role of

247   bacteria in facilitating functional diversity in Symbiodiniaceae is entirely unexplored, but

248   raises intriguing questions about whether the variability of Symbiodiniaceae fitness (and

249   stress resistance) is determined purely by genetic differences between Symbiodiniaceae

250   species (Sampayo et al., 2009; Pettay et al., 2015; Boulotte et al., 2016; Hume et al., 2016;

251   Silverstein et al., 2017; Suggett et al., 2017; LaJeunesse et al., 2018; Liu et al., 2018;

252   González-Pech et al., 2019) or whether other mechanisms play a role.

253   **Dynamic resource exchange supports coral holobiont health and survival**

254   Obligate associations between the cnidarian host and Symbiodiniaceae are essential for coral

255   reef growth and survival. The host coral provides the endosymbionts with substrates for

256   photosynthesis, which in turn fuels the autotrophic production of metabolites that the host

257   cannot synthesise independently (e.g. palmitoleic acid in *Exaiptasia pallida*, (Matthews et al.,

258   2018)). This resource exchange is one of the defining features allowing reef-building corals

259   to flourish in otherwise nutrient-poor environments. Bacteria are also key ecological partners

260   of cnidarians and are increasingly recognised as crucially important for the health of the

261   holobiont (Bourne et al., 2016; Raina et al., 2016; Hernandez-Agreda et al., 2017; Peixoto et

262   al., 2017; Brener-Raffalli et al., 2018) (Fig. 1). Gammaproteobacteria in the genus

263   *Endozoicomonas* are a ubiquitous endosymbiont for corals (Bayer et al., 2013), and

264   comparative genomic analysis of different strains of *Endozoicomonas* from different hosts

265   suggests a common role in carbohydrate cycling and potential specificities in amino acid

266   synthesis (Neave et al., 2017). Recent advances have allowed a better understanding of the

267   functional significance of coral-associated bacterial communities, their roles in resource

268   provision and nutrient cycling (Rädecker et al., 2015; Bourne et al., 2016), their responses to

269   shifts in environmental conditions (Brener-Raffalli et al., 2018), and their potential

270   "probiotic" role in mediating holobiont health and survival (Damjanovic et al., 2017; Peixoto

271   et al., 2017; Webster and Reusch, 2017; Rosado et al., 2019; van Oppen and Blackall, 2019).

272   Only a few studies have specifically considered Symbiodiniaceae-bacterial interactions in the

273   coral holobiont, with their results pointing to the potentially critical role that these

274   partnerships might play in regulating holobiont nutrient cycling and competitive fitness

275   (Ritchie, 2012; Bourne et al., 2013; Ainsworth et al., 2015; Peixoto et al., 2017; Silveira et

276   al., 2017; Bernasconi et al., 2018); Table 1). For example, some coral-associated bacteria can

277   rapidly take up organosulfur compounds released by Symbiodiniaceae cells, such as

278   dimethylsulfoniopropionate (DMSP), to sustain their growth and produce an antimicrobial

279   compound active against common coral pathogens (Raina et al., 2016; Raina et al., 2017).

280   The stability of coral-associated bacterial communities during thermal stress is correlated to

281   the Symbiodiniaceae spp. harboured by the coral host, which potentially affect the

282   susceptibility of the holobiont to bleaching, disease, and colonisation by opportunistic

283   potential pathogens (Littman et al., 2010). Global network analysis of coral holobiont

284   composition has demonstrated that Symbiodiniaceae types co-occur with specific bacterial

285   taxa with phylogenetic affiliation with groups involved in key nutritional pathways (i.e.

286   nitrogen fixation, phosphate production and solubilisation, degradation of DMSP) and/or

287   production of antimicrobial/anti-pathogenic compounds, further supporting the existence of a

288   mutualistic relationship between these microorganisms in the coral holobiont (Ceh et al.,

289   2013; Bernasconi et al., 2018). Furthermore, diazotrophic bacteria provide fixed nitrogen to

290   endosymbiotic Symbiodiniaceae, whereby increased nitrogen availability stimulates high cell

291   division rates by intercellular Symbiodiniaceae, resulting in inorganic carbon sequestration

292   (Lesser et al., 2007; Pernice et al., 2012; Rädecker et al., 2015). Increased transfer of

293   diazotrophically-derived nitrogen to endosymbiotic Symbiodiniaceae and endolithic algae

294   particularly occurs during low availability of external nutrients or during bleaching (Bednarz

295   et al., 2017; Bednarz et al., 2019). Collectively, these insights provide growing evidence that

296   the ecological and metabolic interactions between Symbiodiniaceae and associated bacterial

297   assemblages may be an important feature in maintaining the stability and function of the coral

298   holobiont.

299   **Bacteria-Symbiodiniaceae interactions could be the hidden key for coral reef resilience**

300   Climate change is causing a pandemic of catastrophic "coral bleaching", whereby

301   endosymbiotic Symbiodiniaceae are expelled by their hosts during stressful conditions (Weis,

302   2008). The capacity of reef-building corals to adapt to accelerating global climate change and

303   localised environmental stressors is critical to future coral reef survival (Hoegh-Guldberg,

304   1999; Torda et al., 2017). While the cnidarian host can exhibit stress tolerance through

305   physiological plasticity, the functional capacity of the symbionts also influences holobiont

306   survival. Photo-oxidative mechanisms of bleaching occurs via the physiological collapse of

307   'heat sensitive' Symbiodiniaceae due to severe photosystem damage and the production of

308   harmful reactive oxygen species (ROS), whereby 'heat tolerant' Symbiodiniaceae possess a

309   superior antioxidants system (Warner and Suggett, 2016). In a recent study, the most

310   abundant core member of the Symbiodiniaceae-associated bacterial communities was a

311   member of the *Labrenzia*, a genus of α-proteobacteria also associated with corals and other

312   microalgae cultures (Lawson et al., 2018). A notable function of *Labrenzia* is its ability to

313   produce ROS scavenging-DMSP, and therefore the consistent presence of this bacterium in

314   Symbiodiniaceae cultures potentially supports the DMSP-based antioxidant-system of

315   Symbiodiniaceae. Moreover, the relative abundance of *Labrenzia* differs across

316   Symbiodiniaceae cultures at the genus level (Lawson et al., 2018), and corals harbouring

317   thermally sensitive Symbiodiniaceae (ITS2 type C21a) experienced a reduced abundance of

318   *Labrenzia* in the bacterial community following thermal stress, while corals containing

319   thermally tolerant *Durusdinium trenchii* (ITS2 type D1a) showed an increased in the relative

320   abundance of *Labrenzia* (Grottoli et al., 2018). It is therefore plausible that *Labrenzia* sp.

321   contribute to the observed diversity in antioxidant capacity across Symbiodiniaceae.

322   Furthermore, bacterial communities are able to regulate the coral holobionts' external levels

323   of the reactive oxygen species superoxide which may contribute to pathogen resistance (Diaz

324   et al., 2016); symbiotic bacteria associated with Symbiodiniaceae could therefore provide a

325   similar mechanism of protection.

326   These results raise a provocative hypothesis that bacteria might in fact be partially

327   responsible for some traits previously solely ascribed to Symbiodiniaceae, and more

328   importantly, that some of these traits may play a role in the stability of coral-symbiont

329   associations. Again, such a notion emphasizes the critical need to consider bacterial dynamics

330   and resource exchange when examining Symbiodiniaceae functional diversity.

331   **Concluding Remarks**

332   Unravelling the significance of the associated bacteria on Symbiodiniaceae health and

333   functional diversity provides a conceptual shift in the factors determining the resilience of

334   coral reef organisms to survive in a changing ocean, with wider implications for

335   understanding algal–microbial interactions in extreme environments. We argue that

336   systematic study of bacterial-Symbiodiniaceae interactions is crucial, not least because a

337   detailed understanding of the associated bacterial functions is imperative for conservation and

338   restoration approaches leveraging the microbiome to alter host phenotype (van Oppen et al.,

339   2015; Peixoto et al., 2017; Morgans et al., 2019). Addressing these critical gaps in our

340   knowledge is only now possible as a result of technological advances allowing for the

341   manipulation of Symbiodiniaceae-bacterial assemblages, and for examination of

342   microorganism metabolic interactions. For example, localisation and identification of the

343   bacteria associated with Symbiodiniaceae in the free-living and endosymbiotic state could be

344   achieved using a combination of fluorescent *in situ* hybridisation (FISH), laser

345 microdissection, pure culturing, and 16S rRNA gene sequencing. Imaging techniques, such as

346 transmission electron microscopy, have been applied to investigate viral-mediated coral

347 bleaching and disease (Wilson et al., 2001; Davy et al., 2006) and have the potential to be

348 applied to observe Symbiodiniaceae-bacteria associations. Molecular exchange can be

349 measured and visualised at the cellular level using stable isotopic labelling combined with

350 nanoscale secondary-ion mass spectrometry (NanoSIMS) (Raina et al., 2017). Identification

351 and quantification of key metabolites and metabolic pathway activity could be achieved with

352 the integration of metabolomic and transcriptomics analyses, as was recently applied to

353 elucidate mechanisms underlying symbiont compatibility in the Aiptasia-Symbiodiniaceae

354 symbiosis (Matthews et al., 2017). Phylogenetic and gene expression analyses of coral-

355 associated fungi revealed a diverse and metabolically active community associated with a

356 coral holobiont, and these analytical approaches could be applied to Symbiodiniaceae-

357 bacteria associations (Amend et al., 2012). Metagenomics and interaction networks could be

358 used to help predict Symbiodiniaceae-bacteria interactions, as was successfully applied to

359 infer phage-bacteriophage interactions in bleached and diseased corals (Soffer et al., 2015).

360 Metabolic pathway analysis can be used to study the flexibility in metabolic networks and has

361 been applied to reveal nutritional provisioning requirements in the *Planococcus citri*

362 (mealybug)-bacteria symbiosis (Hanson et al., 2014); thus, there is enormous potential for

363 employing metabolic pathway analysis of the coral holobiont to predict a system-wide

364 integrated response to changes in the environment (Suggett and Smith, 2019). However,

365 several important challenges remain, including identifying the genomes of the bacteria in

366 cultured Symbiodiniaceae, and the generation of robust axenic Symbiodiniaceae cultures that

367 can be used for co-growth experiments in order to characterise the functional interactions of

368 specific bacterial strains. Another challenge, when investigating interactions under laboratory

369 conditions is that the composition of bacteria communities of cultured Symbiodiniaceae

370   strains may not reflect wild populations, because of experimental procedures or

371   acclimatisation to laboratory conditions. Overcoming these challenges will potentially usher a

372   critical new era that will enable resolving the metabolic interactions at the heart of coral reef

373   symbioses. Research directed to exploring Symbiodiniaceae-bacterial interactions will

374   provide desperately needed new grounds with which to understand how multi-partner

375   resource exchange amongst the coral holobiont regulates fitness and resilience of reef

376   ecosystems to rapidly changing environmental conditions.

377

378   **Competing interests**

379   We declare we have no competing interests.

380

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387

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