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REVIEW

Symbiosis: the other cells in development

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ABSTRACT

Animal development is an inherently complex process that is regulated by highly conserved genomic networks, and the resulting phenotype may remain plastic in response to environmental signals. Despite development having been studied in a more natural setting for the past few decades, this framework often precludes the role of microbial prokaryotes in these processes. Here, we address how microbial symbioses impact animal development from the onset of gametogenesis through adulthood. We then provide a first assessment of which developmental processes may or may not be influenced by microbial symbioses and, in doing so, provide a holistic view of the budding discipline of developmental symbiosis.

KEY WORDS: Microbiota, Embryogenesis, Evolution, Stem cells, Regeneration, Animal-microbe, Symbiosis

Introduction

How an egg cleaves, cells differentiate and tissues form three-dimensional structures are inherently complex processes that have been central to developmental biology for more than a century (Waddington, 1956). These morphogenic events are regulated by highly conserved genomic networks that use intrinsic signals that encode the embryonic and adult body plans (Davidson and Erwin, 2006; Gilbert et al., 1996). Crucial information is simultaneously received from the environment, and the interpretation of these extrinsic signals enables plasticity in the developmental phenotype (Gilbert, 2001; West-Eberhard, 2003). Conceptually integrating embryology, evolution and ecology has allowed development biology to be studied in a more natural setting, but this framework often precludes how microbial symbionts influence development (Bosch and McFall-Ngai, 2021; Gilbert et al., 2015; McFall-Ngai, 2002).

Microorganisms (e.g. archaea, bacteria, fungi and viruses) live freely between cells, on the cell surface, in the cytoplasm and within specialized cytoplasmic compartments (Bright and Bulgheresi, 2010). They inhabit most somatic tissues as well as the germline of all major animal lineages (Fig. 1; Table S1; Bright and Bulgheresi, 2010; McFall-Ngai et al., 2013; Zilber-Rosenberg and Rosenberg, 2008). Their abundance is often on the same order of magnitude as animal cells and this relationship scales allometrically with host mass (Kieft and Simmons, 2015; Sender et al., 2016). Symbiotic microbes are thus omnipresent and their functional importance to animal biology is deeply rooted in the evolutionary and ecological origins of host immunity, metabolism and neurology (Hentschel et al., 2012; Klimovich et al., 2020; McFall-Ngai et al., 2013; Thaiss et al., 2016). Microbial symbionts are also necessary – and even essential – for fundamental aspects of development (Bosch and McFall-Ngai, 2021; Fraune and Bosch, 2010; Gilbert, 2016; Gilbert et al., 2015; McFall-Ngai, 2002).

Symbioses between animal hosts and microbes (i.e. these 'other' cells) have had an ongoing developmental partnership for at least 600 million years (Carrier et al., 2022; McFall-Ngai, 2002). The realization, however, that development is an intricate chemical and morphological dance between instructions in the animal genome, the microbial symbionts and the environment has only recently been recognized (Bordenstein and Theis, 2015; Carrier and Reitzel, 2017; McFall-Ngai, 2014; Ye and Rawls, 2021). The importance of symbiotic microbes to development and the need for a conceptual shift has been best articulated by McFall-Ngai and Ruby (1991): 'Animal developmental biology, while typically concerned with the essential processes of differential control of gene expression and signaling between developing cells of a single organism, must also be concerned with the fact that, in nature, organisms often develop normally only in the presence of associated microorganisms.'

This Review aims to explain how symbiotic microbes influence development and to differentiate between processes that are and are not currently known to be impacted by these partnerships. In doing so, we provide a holistic view of development and postulate that symbiosis is a ubiquitous component of animal development.

Microbes during embryogenesis

Coordination between an animal host and microbial symbionts during reproduction and development can be found among the oldest extant animal lineages (Comizzoli et al., 2021; Rowe et al., 2020). Marine sponges, for example, form symbioses with microbes from diverse phylogenetic lineages that densely populate the periphery of the oocyte at the onset of vitellogenesis and are transmitted to the cytoplasm through a combination of endocytosis, phagocytosis and nurse cells via transient cytoplasmic bridges (Fig. 2A; Carrier et al., 2022; Maldonado, 2007). Microbes, and the specialized architecture to transmit them, have since been found in the germline and during developmental stages of every major animal group (Fig. 1; Table S1; Bright and Bulgheresi, 2010; Eckelbarger and Hodgson, 2021; McFall-Ngai, 2002). In this section, we summarize how symbionts reach the offspring, their known functions during embryonic and larval development, and the consequences of their removal.

From mother to offspring

Symbioses can be maintained with high fidelity through the female germline. Transovarian (vertical) transmission is ancient and evolutionarily advantageous, and occurs for single symbionts as well as diverse prokaryotic communities (Bright and Bulgheresi, 2010; McFall-Ngai, 2002). This type of transmission often uses the vitellogenic machinery to regulate which microbial lineages are incorporated into the oocyte (Bright and Bulgheresi, 2010; McFall-Ngai, 2002; Nyholm, 2020). For example, the endosymbiont *Spiroplasma poulsonii* enters the germline of the fruit fly *Drosophila melanogaster* late in oogenesis alongside yolk granules, and the loss of function of the vitellogenic factor *yolkless*

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Development (2022) 149, dev200797. doi:10.1242/dev.200797

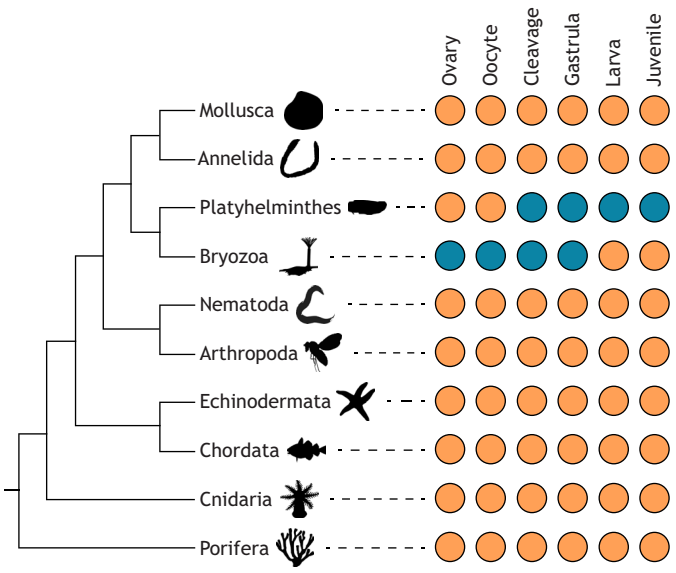

Fig. 1. Animal phylogeny and developmental symbiosis. Microbial prokaryotes are present (orange circles) in the reproductive and developmental stages of all major animal lineages (i.e. the ten with the most known species; this does not include the early-diverging ctenophores, of which no studies were found), with Bryozoa and Platyheminthes being exceptions. This is not due to their absence (blue circles), but that these stages have yet to be investigated. The simplified phylogeny was modeled according to Dunn et al. (2008). All organism silhouettes are from PhyloPic (www.phylopic.org). Related references can be found in Table S1. Note that 'ovary' is used as a general term to describe the reproductive system in animals.

inhibits this transmission (Fig. 2B; Herren et al., 2013). If microbial cells are not transmitted into the cytoplasm, then they may be deposited onto the external surface of the eggs by specialized morphological features of the adult (Bright and Bulgheresi, 2010; Flórez and Kaltenpoth, 2017; Nyholm, 2020). The spatial localization and abundance of microbial cells is also regulated. The deep-sea clam *Calyptogena okutanii* deposits ∼400 cells of an intracellular symbiont at the vegetal pole of each oocyte, while ∼34,000 endosymbiont cells are dispersed between yolk granules in oocytes of the sea urchin *Heliocidaris erythrogramma* (Carrier et al., 2021; Ikuta et al., 2016).

Microbes are not restricted to being vertically transmitted during oogenesis. Instead, symbionts may be inherited at any point during the developmental window where the parent and offspring are in contact. The paths taken by microbes during this developmental window are remarkably diverse and reflect the life-history tendencies of the host (Bright and Bulgheresi, 2010; McFall-Ngai, 2002). For example, bacterial symbionts can migrate through cleavage furrows and into the extracellular space between blastomeres in marine sponges (Riesgo et al., 2007). Symbionts can also be endocytosed at the blastula–bacteriocyte interface in aphids (Brough and Dixon, 1990; Koga et al., 2012), can be selectively recruited from an egg capsule during embryogenesis by earthworms, salamanders and stinkbugs (Bishop et al., 2021; Davidson and Stahl, 2008; Kaiwa et al., 2014), and can be harvested by adult ascidians and spread onto the brooded larva as it is released (Hirose, 2015).

Once within the embryo, these microbial cells can coordinate with the cellular machinery of the host to establish anterior-posterior polarity and move throughout the developing embryo. Cells of the intracellular bacterium *Wolbachia* spp., for example, actively migrate towards the posterior pole of *D. melanogaster* embryos using microtubules, dynein and kinesin to inhabit the primordial germ cells that later differentiate into the female germline (Ferree et al., 2005; Landmann et al., 2014, 2010; Russell et al., 2018; Serbus and Sullivan, 2007; Strunov et al., 2022). Once in the female germline, *Wolbachia* spp. cells can enhance the maintenance of germline stem cells by excreting proteins that interact with RNA-binding proteins essential for germ cell maintenance (e.g. Nanos but not Vasa), and can increase the division rate of host cells to increase oocyte production (Fast et al., 2011; Ote et al., 2016). Similarly, *Wolbachia* spp. can excrete prophage proteins that modify the histone-protamine transition during spermatogenesis and influence embryonic success (Horard et al., 2022; Kaur et al., 2022).

From environment to offspring

Animal-microbe symbioses can also be maintained through horizontal acquisitions. This type of transmission occurs when a symbiosis is non-continuous throughout the host life cycle and resumes following an environmental acquisition. Most often the aposymbiotic phase precedes the symbiotic phase, such that the germline and early-stage embryos lack microbes, while larvae and/or juveniles are symbiotic. Similar to being inherited through the germline, horizontal transmissions are ancient, evolutionarily advantageous and can be maintained with high fidelity (Bright and Bulgheresi, 2010; McFall-Ngai, 2002). Acquiring symbionts from the environment is more common in aquatic habitats than on land because water is relatively viscous (Purcell, 1977; Russell, 2019; Vogel, 1994). This property allows for taxonomically rich communities of microbial cells to remain suspended in the water column and, in turn, requires an elaborate communication between host and symbiont(s) to distinguish between friend and foe (Azam and Malfatti, 2007; Nyholm and Mcfall-Ngai, 2004). Despite ontogenetic and ecological differences in when and how microbial symbionts are acquired, this transmission mode remains equally important to development.

The most well-studied example of horizontal transmission is that of the bobtail squid *Euprymna scolopes* and the bacterium *Vibrio fischeri* (Fig. 2C). In this partnership, embryonic squid lack symbionts until a few *V. fischeri* cells are recruited from the seawater after hatching. *E. scolopes* and *V. fischeri* then undergo an extensive dialog to induce morphogenesis of the light organ (Nyholm and McFall-Ngai, 2021; Vicick et al., 2021). Similarly, chemoautotrophic symbionts of the deep-sea annelid *Riftia pachyptila* are acquired post-metamorphosis at hydrothermal vents and these bacteria then contribute to inducing morphogenesis of the trophosome, the organ that houses symbiotic bacteria and provides the host with nutrients (Nussbaumer et al., 2006). Horizontal transmissions, however, do not always entail inducing an extensive morphogenic event. Embryos of the sea urchin *Strongylocentrotus purpuratus* associate with relatively few bacterial cells from diverse lineages. Bacteria then flood the maturing gut lumen upon hatching, after which the microbiome associated with these larvae diverges from the environmental microbiota through, what is hypothesized to be, a host-mediated selection. Many of these microbial cells then remain associated with the host after metamorphosis (Carrier and Reitzel, 2019a; Schuh et al., 2020).

Recruiting symbionts from the environment during embryogenesis, as part of a restructuring of the microbiome, is also a widely used strategy for acclimating to abiotic factors (Carrier and Reitzel, 2017; Kohl and Carey, 2016). Several species of echinoderm larvae, for example, exhibit bi-directional shifts in the composition of their bacterial community in response to food availability (Carrier and Reitzel, 2018). Larvae of the coral

Development (2022) 149, dev200797. doi:10.1242/dev.200797

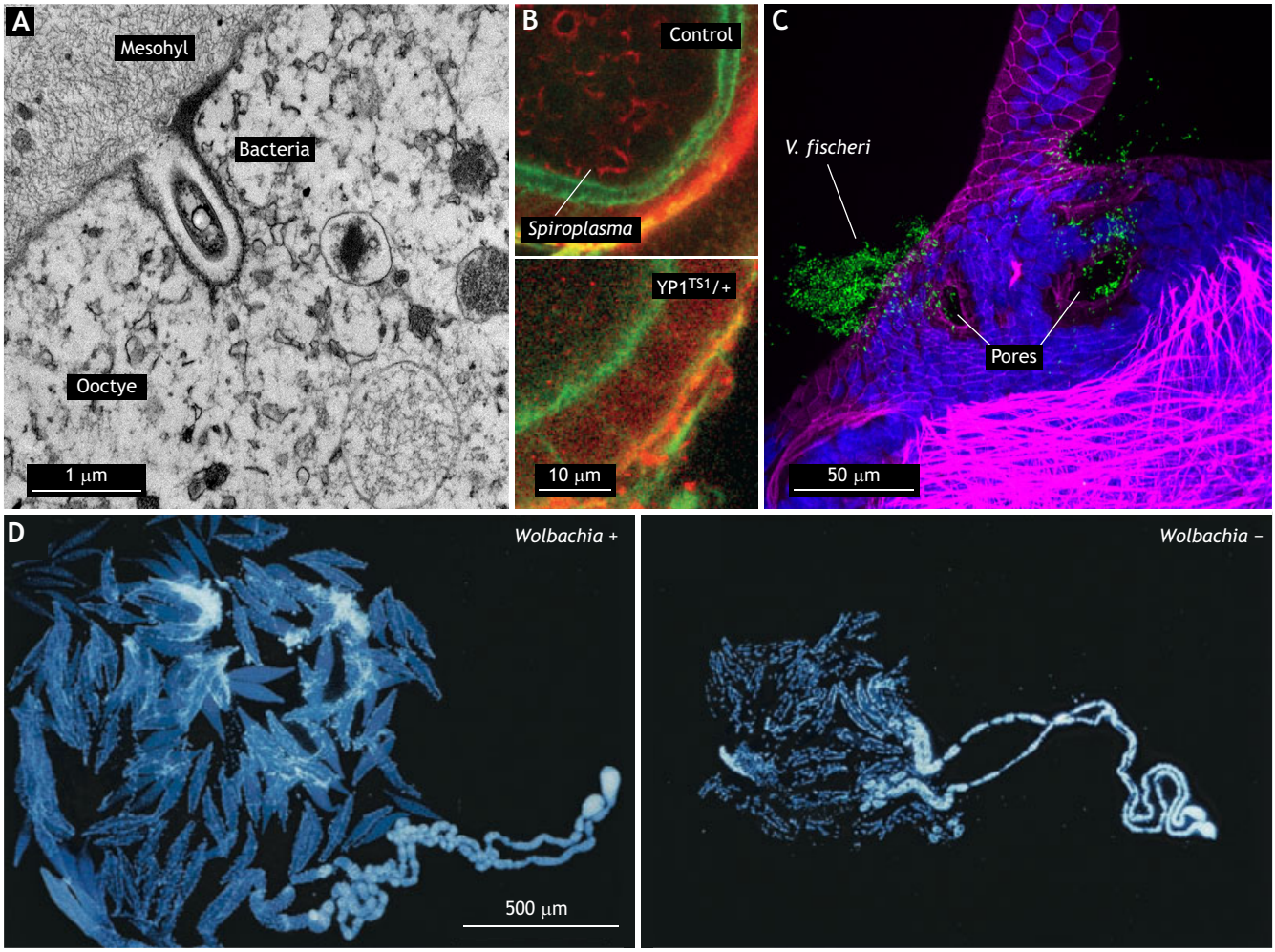

Fig. 2. Examples of developmental symbioses and symbiont transmission. (A) Vertical transmission by phagocytosis of a bacterium from the mesohyl of the sponge *Corticium candelabrum* to a young oocyte, as visualized by transmission electron microscopy. Reproduced, with permission, from Riesgo et al. (2007). (B) The involvement of yolk proteins in endosymbiont transmission in the fruit fly *Drosophila melanogaster*, whereby cells of *Spiroplasma poulsonii* (red; anti-DW1 antibody against strain DW-1T) are transmitted in control embryos (top) and much less frequently in Yolk protein 1 mutants ($YP1^{TS1/+}$; bottom). Reproduced from Herren et al. (2013), where it was published under a CC-BY 4.0 license. (C) Horizontal transmission of the bacterium *Vibrio fischeri* (labeled with GFP) from outside the pores of a juvenile bobtail squid *Euprymna scolopes* (blue, DAPI; magenta, actin). Courtesy of Dr Tara Essock-Burns and Dr Margaret McFall-Ngai. (D) Experimental removal of the endosymbiont *Wolbachia* spp. by the antibiotic rifampicin reduces ovary size in the parasitoid wasp *Asobara tabida* (stained with DAPI). Reproduced from Dedeine et al. (2001), where it was published under a CC-BY 4.0 license.

Acropora gemmifera, on the other hand, can recruit microbes from the environment in response to seawater acidification (Zhou et al., 2017). If this environmental reservoir is depleted, then the acclimation response of the host can be reduced. The removal of environmental microbes impairs mitochondrial enzyme activity and this, in turn, limits the thermal niche of tadpoles of the frog *Lithobates clamitans* (Foutaine et al., 2022). Thus, microbes that are horizontally acquired from the environment can contribute to the ecological activity of the developing animal host (Carrier and Reitzel, 2017; Gilbert et al., 2015).

Transitions during development

One of the most prevalent themes in developmental symbiosis is that microbial symbionts are key elements of transitions between stages, phenotypes and modes. Species from diverse animal groups [e.g. the freshwater polyp *Hydra vulgaris* (Fraune et al., 2010), zebrafish *Danio rerio* (Stephens et al., 2016) and primate *Homo sapiens* (Charbonneau et al., 2016; Koenig et al., 2011)] exhibit successions in community composition, titer and spatial location during embryogenesis (and through to adulthood) (Strunov et al., 2022). In animals that exhibit developmental and morphological plasticity, shifts in the associated bacterial community precede and then correlate with the expression of the environmentally elicited phenotype (Carrier and Reitzel, 2018; 2019b). The loss of this phenotype-specific microbiome can follow an evolutionary switch in developmental mode, which co-occurs with a reduction in the diversity and abundance of the microbiome (Carrier et al., 2021; Strathmann, 1985). Such switches in developmental life-history may be mediated by microbes. It has recently been hypothesized that the switch from feeding (planktotrophy) to non-feeding (lecithotrophy) in the sea urchin genus *Heliocidaris* is induced by an endosymbiont that manipulated host reproduction and development to favor its transmission (Carrier et al., 2021; Kustra and Carrier, 2022). Last, a network of lipid signaling molecules derived from the environmental bacterium *Algoriphagusma chipongonensis* regulates whether solitary choanoflagellate cells develop into a multicellular 'rosette' colony, which subsequently enables the transition from asexual

Development (2022) 149, dev200797. doi:10.1242/dev.200797

proliferation to sexual reproduction (Levin and King, 2013; Woznica et al., 2016).

Development can remain dependent on microbes through the final moments as a larva and in the transition into a juvenile. Embryos of the sponge *Amphimedon queenslandica* inherit three dominant symbionts, which biosynthesize arginine that is then taken up by larval cells to produce nitric oxide and to hormonally induce metamorphosis (Fieth et al., 2016; Song et al., 2021). Similarly, symbiont-derived tyrosine regulates metamorphosis and stimulates cuticle formation in some insects (Hammer and Moran, 2019; Kiefer et al., 2021; Rewitz et al., 2009). Microbes that form environmental biofilms are also capable of inducing life-stage transitions (Cavalcanti et al., 2020; Hadfield, 2011). Larvae of the polychaete *Hydroides elegans* must come in contact with a specific bacterium (*Pseudoalteromonas luteoviolacea*) that uses a contractile injection system to mechanically initiate diacylglycerol, protein kinase C and mitogen-activated protein kinase signaling, and induce the host to transition onto the seafloor (Ericson et al., 2019; Malter et al., 2022; Shikuma et al., 2014). This collection of examples points towards microbial symbionts being causal agents of major transitions, but how does embryogenesis progress if these symbionts are removed?

Removing microbial cells

Whether inherited by the female germline or acquired from the environment, the reduction or removal of microbial cells can have a substantial impact on reproduction and development. The extent to which developmental processes are disrupted often depends on whether the symbiosis is obligate or facultative (McCutcheon and Moran, 2012; Moran et al., 2008). Removal of obligate endosymbionts at different stages of reproduction and development can inhibit oocyte production, reduce oocyte size, and decrease larval growth and survival (Fig. 2D; Dedeine et al., 2005, 2001; Douglas, 1996; Lee et al., 2017; Pannebakker et al., 2007; Sison-Mangus et al., 2015). Reduction of (what are presumed to be) facultative symbionts in the moon jelly *Aurelia aurita* halts asexual reproduction (i.e. strobilation and ephyra release), while the feeding arms of sea urchin (*Strongylocentrotus purpuratus*) larvae exhibit an elevate growth rate (Schuh et al., 2020; Weiland-Bräuer et al., 2020). Moreover, microbial depletion can also lead to the offspring being more susceptible to pathogens, whereby exposure to *Vibrio* spp. causes developmental malformations and an increased mortality in *A. aurita*, and inflammation of the midgut epithelium and ectodermal lysis in *S. purpuratus* (Schuh et al., 2020; Weiland-Bräuer et al., 2020).

Independent of the degree of symbiotic intimacy between an animal host and their microbiota, manipulating the host-associated microbial community can affect embryogenesis and larval development in ways specific to host life-history (Metcalf et al., 2019). First, larvae of the parasitoid wasp *Nasonia vitipennis* exhibit a compositional shift in their bacterial community when entering diapause, and the removal of these symbionts makes this developmental and metabolic quiescence unsustainable (Dittmer and Brucker, 2021). Second, manipulating the presence of and interactions between maternal bacterial lineages influences the developmental pace (from embryo to pupae), lifespan and reproductive strategy of *Drosophila melanogaster*, while the mosquito *Aedes aegypti* is unable to develop past the first instar stage (Coon et al., 2014; Gould et al., 2018). Last, the bacterium *Alteromonas* sp. produces organic compounds (isatins) that protect brooded embryos of the shrimp *Palaemon macrodactylus* from the fungus *Lagenidium callinectes*, and the removal of this defensive symbiont prohibits development (Gil-Turnes et al., 1989). By reducing or removing these microbial symbionts, the offspring deviates from a familiar developmental trajectory and instead exhibits a phenotype similar to that of a genetic manipulation (Bordenstein and Theis, 2015).

Host-microbe interactions post-embryogenesis

Post-embryonic development involves the extensive growth, patterning and maintenance into and of the adult form, and microbial symbionts also influence these processes. The most widely recognized interaction occurs in the gastrointestinal tract of a diverse array of animal species (Rawls et al., 2004; Ye and Rawls, 2021). Microbes colonize the gut during early gastrulation and remain engaged in an intimate dialog with the host throughout adulthood (Solis et al., 2020; Ye and Rawls, 2021). Despite decades of intense study on which microbial lineages reside in the gut, their metabolic capabilities and general patterns of assembly (Brooks et al., 2016; Groussin et al., 2017; Song et al., 2020), we know relatively little about the developmental implications of these symbionts post-embryogenesis. Much of our understanding has been obtained by comparing wild-type and gnotobiotic individuals of various animal models, including the rodent *Mus* spp., *Drosophila melanogaster* and *Danio rerio* (Ye and Rawls, 2021); however, on-going research has begun to use a wider diversity of animal species. Efforts to date support the view that microbial symbionts are necessary, and often essential, for three processes: cell and tissue differentiation, immune priming and regulation, and neurogenesis.

Cell and tissue differentiation

Intestinal epithelial cells in vertebrates remain largely undifferentiated under germ-free conditions, whereby they are metabolically impaired, genetically and epigenetically unstable, and disengaged in the immune system. Subsequent exposure to gut microbiota causes tissue-wide changes in gene expression, methylation and topography (Pan et al., 2018; Russell and Castillo, 2020; Ye and Rawls, 2021). This symbiont-mediated differentiation occurs for several cell types, including enterocytes, enteroendocrine cells, goblet cells, M-cells and Paneth cells (Ye and Rawls, 2021). For example, stem cells in the gut of *D. rerio*, which serve as precursors of secretory cells, are unable to differentiate due to a disruption in Myd88-dependent signaling of Notch, but resume their developmental trajectory when exposed to the natural gut microbiota (Fig. 3A; Bates et al., 2006; Cheesman et al., 2011; Troll et al., 2018). Microbe-mediated differentiation of host tissues is not restricted to the gut (Fronk and Sachs, 2022). The bioluminescent bacterium *V. fischeri* stimulates light-organ development in the squid *Euprymna scolopes* (Nyholm and McFall-Ngai, 2021; Vicick et al., 2021), an uncharacterized γ-proteobacteria of the stinkbug *Plautia stali* transforms a simple and smooth 'midgut' into an elaborate symbiotic organ (Oishi et al., 2019), and the acquisition of endosymbionts by various benthic marine invertebrates from chemosynthetic environments induces morphogenesis of nutritional organs (Dubilier et al., 2008; Franke et al., 2021; Nussbaumer et al., 2006).

Gut-associated microbes also influence the rate of host cell proliferation. The generation time of epithelial cells in the colonic crypts of germfree *Mus* spp. is 1.7× shorter than that of conventionally raised siblings (Nowacki, 1993), and this can be restored when inoculated with their natural microbiota (Lee et al., 2018b). Similar patterns have also been observed in *D. melanogaster* (Buchon et al., 2009), *D. rerio* (Cheesman et al., 2011) and *H. sapiens* (Dougherty et al., 2020). Within the gut, the rate of epithelial cell production increases towards the distal part of the intestine, which correlates with the abundance of microbes (Kaunitz and Akiba,

Development (2022) 149, dev200797. doi:10.1242/dev.200797

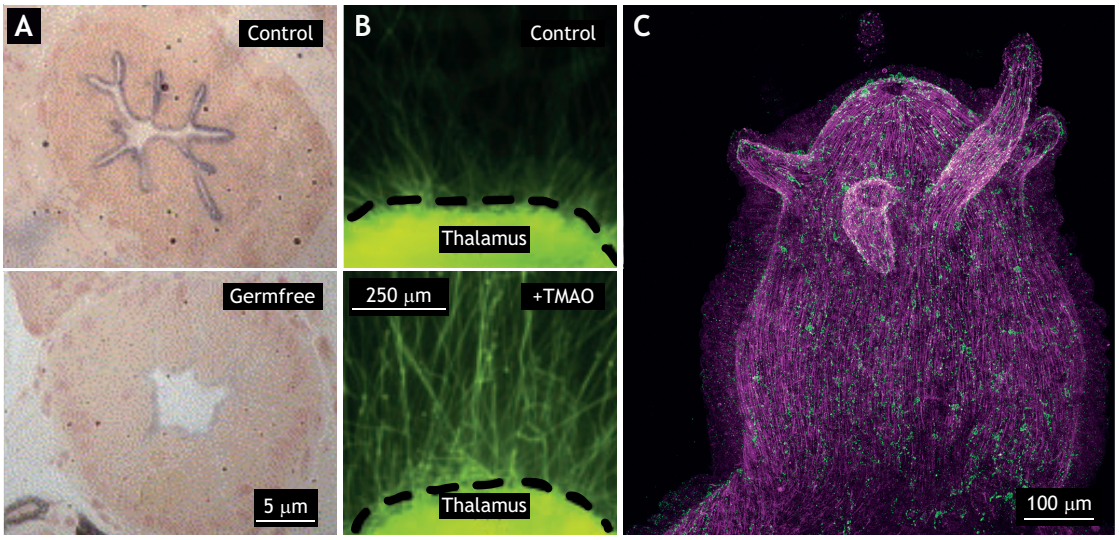

Fig. 3. Examples of the role of microbial symbionts in tissue maturation. (A) The microbiome plays a major role in gut activity, as shown here with alkaline phosphatase activity (blue) in the gut of the zebrafish *Danio rerio* that have been cultured in control (top) and germ-free (bottom) conditions. Reproduced, with permission, from Bates et al. (2006). (B) Maternal microbiota stimulate axon growth in the brain, whereby thalamic explants exposed to the maternal microbial metabolite trimethylamine-*N*-oxide (TMAO; bottom) exhibit an elevated level of axonogenesis compared with the controls (top). Reproduced, with permission, from Vuong et al. (2020). (C) The nerve net of *Hydra vulgaris* expresses the *Hydra*-specific Hym355 neuropeptide (an antimicrobial agent; green). Muscular fibers of epithelial cells are labeled in magenta. Reproduced from Giez et al. (2021), where it was published under a CC-BY 4.0 license.

2019). One pathway known to be involved microbe-mediated proliferation of host cells is Wnt signaling. The loss-of-function of axin 1 increases cell proliferation in the gut of wild-type, but not germ-free, individual *D. rerio*. This, however, could be restored by mono-colonizing the gut with the resident bacterium *Aeromonas veronii*, which upregulates Wnt signaling and β-catenin protein levels (Bates et al., 2006; Cheesman et al., 2011; Troll et al., 2018). Similarly, the bacterium *Lactobacillus plantarum* stimulates the generation of reactive oxygen species that induce proliferation of intestinal epithelial cells in *D. melanogaster* (Reedy et al., 2019).

The mechanisms that underpin animal development are vastly similar to those required for compensatory growth, wound healing and regeneration (Brockes and Kumar, 2008; Tanak and Reddien, 2011). Microbial symbionts exert their influence on regenerative processes in a manner similar to that of post-embryonic development. Following the expulsion of the internal organs (evisceration) by sea cucumbers, the gut microbiome exhibits a deterministic community-level succession that correlates with tissue differentiation (Díaz-Díaz et al., 2022; Weigel, 2020). Similar to proliferation in the gut, the host-associated bacteria produce small molecules (indoles) that regulate the expression of the Wnt pathway and signaling of the immune response gene *Myd88* that mediates regeneration in the planarian *Dugesia japonica* and *Mus* spp., respectively (Lee et al., 2018a; Wang et al., 2021). Moreover, in *D. japonica*, microbial metabolites modulate host gene expression that instruct anterior-posterior axis formation and organ formation (Williams et al., 2020). Finally, microbes on the epidermis of *H. sapiens* can form a biofilm, modulate the immune response (by regulating host gene expression and suppressing pathogens) and influence proliferation (Byrd et al., 2018; Tomic–Canic et al., 2020). Microbes therefore play an essential role in an array of processes related to the differentiation of host tissues (Sommer and Bäckhed, 2013; Ye and Rawls, 2021).

Immune priming and regulation

Microbes that mediate cell proliferation and tissue differentiation often inhabit the mucosal surface of animal guts and, in doing so, play a myriad of roles in immunity (Thaiss et al., 2016). In fact, the need of the host to recognize and manage complex and species-specific symbiont communities is believed to have been a major selective pressure underlying the evolution of both innate and adaptive immunity (Bosch, 2014; McFall-Ngai, 2007; Reshef et al., 2006). These host-microbe interactions have several widespread implications for post-embryonic development, with the most predominant being that microbial symbionts are essential for the maturation of a variety of immune cell types, that microbial compounds shape these interactions across host generations and that microbial symbionts actively protect against pathogenic invasions (Fraune et al., 2015; Kamada et al., 2013; Round and Mazmanian, 2009; Ye and Rawls, 2021). Our understanding of the role that microbes play in immune maturation stems from a select few experimental systems from comparisons between wild-type and germ-free individuals, but also from transplanting microbial communities between host species (e.g. Brooks et al., 2016; Chung et al., 2012).

Owing to the importance of maternal symbiont transmission (Bright and Bulgheresi, 2010) and impact of a modern lifestyle on the microbiome (Sonnenburg et al., 2016; Yatsunenko et al., 2012), the most widely discussed impact of microbes on immune development is in *H. sapiens* born by caesarean section instead of vaginally. When born by caesarean section, the offspring lack many of the natural members of the microbiome and this leads to an underdeveloped immune system (Koren et al., 2012; Sandall et al., 2018). Depleting the host of gut microbiota or transplanting host-specific microbial communities between host species can have a similar effect on the maturation of animal immunity (Zheng et al., 2020a). For example, *Mus* spp. that lack maternal microbiota have lower expression levels of microbe-mediated epithelial antibacterial peptides that shape the adult immune system (de Agüero et al., 2016). Similarly, *Mus* spp. colonized by human microbiota have ten times fewer T cells and an immune cell profile more similar to germ-free *Mus* spp. than to wild-type individuals (Chung et al., 2012). This trend is seen for diverse cell types throughout the gut (e.g. myeloid and lymphoid cells) (Thaiss et al., 2016).

Development (2022) 149, dev200797. doi:10.1242/dev.200797

The influence of microbes on host immunity is more widespread than the gut. For example, microbially derived antigens that are produced in the gut can be trafficked throughout the body, which, in turn, induces the expansion of microbiota-specific T cells. Once in the periphery, microbiota-specific T cells have pathogenic potential or can protect against related pathogens. In this way, the developing microbiota shapes and expands the T-cell repertoire, allowing enhanced recognition of intestinal microorganisms and pathogens (Zegarra-Ruiz et al., 2021). These microbe-elicited effects on host immunity can be actively maintained between generation. In *H. sapiens*, maternal commensal microbiota invoke protective antibodies that can be delivered through breast milk to protect against pathogens and prime the body for colonization of resident symbionts (Thaiss et al., 2016; Zheng et al., 2020b). This trans-generational maintenance of host immunity is hypothesized to be more widespread. Microbial symbionts therefore appear to be essential in the maturation of host immunity during development.

Central to the nervous system

A growing theme in animal-microbe symbiosis is that microbes shape the development of the nervous system (Eisthen and Theis, 2016; Klimovich and Bosch, 2018; Sharon et al., 2016). The central nervous system has attracted most of this attention due to its involvement in higher cognitive function. Specific microbial lineages can be spatially restricted to neuroblasts and neurons, and deficiencies in learning, memory, recognition and emotional behaviors can occur when these microbes are depleted (Foster et al., 2017; Gareau, 2014; Strunov et al., 2022). This appears to be caused by the lack of microbe-influenced host gene expression that is involved in the formation of new axons within the neurons. In particular, axons that connect the thalamus and cortex of the brain are reduced in number and length in the absence of microbes, and those that are present exhibit a reduced excitability (Fig. 3B; Vuong et al., 2020). The mechanisms by which microbial signals contribute to neurogenesis are poorly understood in comparison with tissue differentiation and immunity, but current evidence supports that microbes can also regulate this process. In *Mus* spp., tryptophan-metabolizing gut microbes secrete indoles that promote neurogenesis in the hippocampus (Wei et al., 2021), which contributes to the formation of an axis between the brain, gut and microbiome (Cryan et al., 2019). On the contrary, the endosymbiont *Spiroplasma poulsonii* can severely disrupt neurogenesis in *Drosophila melanogaster* by secreting a toxin that prohibits neuroblast differentiation and altering host behavior (Harumoto and Lemaitre, 2018; Martin et al., 2013).

The relationship between neurogenesis and microbes is more evolutionarily ancient than the central nervous system, as this integration is particularly pronounced in animal species without this centralization (Cryan et al., 2019; Klimovich and Bosch, 2018). Microbes live in close proximity to the diffuse nerve net of the freshwater polyp *Hydra vulgaris*, allowing the population of prototypical pacemaker neurons to interact with microbes. The neuropeptides Hym-357 and Hym-370, for example, can actively regulate the spatial structure of the resident microbiota (Fig. 3C; Giez et al., 2021; Klimovich and Bosch, 2018; Klimovich et al., 2020). By depriving *H. vulgaris* of its microbial symbionts, this nerve net is dwarfed and normal behaviors (e.g. spontaneous body contractions) become less frequent (Ezenwa et al., 2012; Klimovich et al., 2020; Murillo-Rincon et al., 2017). How microbes actively regulate the enteric nervous system remains unknown. One general expectation

Table 1. Developmental processes in which microbial symbionts are or are not currently known to be involved

Category	Process	Are microbes involved?	Direct or Indirect?	Representative reference(s)
Gametogenesis	Oogenesis	Yes	Direct	Dedeine et al. (2001, 2005)
	Vitellogenesis	Yes	Direct	Herren et al. (2013); Lee et al. (2017)
	Spermatogenesis	Yes	Direct	Horard et al. (2022); Kaur et al. (2022)
	Spawning	Unknown	N.A.	N.A.
Embryogenesis	Fertilization	Hypothesized	N.A.	Carrier et al. (2021)
	Polyspermy block	Unknown	N.A.	N.A.
	Pronuclear fusion	Unknown	N.A.	N.A.
	Cleavage	Unknown	N.A.	N.A.
	Blastulation	Unknown	N.A.	N.A.
	Gastrulation	Hypothesized	N.A.	Nyholm and McFall-Ngai (2014)
	Larval development	Yes	Direct	Gould et al. (2018); Rabatel et al. (2013)
	Metamorphosis	Yes	Direct	Shikuma et al. (2014); Song et al. (2021)
Cellular activity	Anterior-posterior polarity	Yes	Direct	Landmann et al. (2014)
	Apoptosis	Yes	Direct	Harumoto et al. (2016)
	Cell-cell adhesion	Yes	Direct	Woznica et al. (2016)
	Gene regulatory networks	Yes	Indirect	Russell and Castillo (2020)
	Transcription	Yes	Direct	Moriano-Gutierrez et al. (2020)
	Translation	Unlikely	N.A.	Hansen and Moran (2012)
Differentiation	Dorsoventral patterning	Unknown	N.A.	N.A.
	Immunogenesis	Yes	Direct	Chung et al. (2012)
	Neurogenesis	Yes	Direct	Klimovich et al. (2020)
	Organogenesis	Yes	Direct	McFall-Ngai and Ruby (1991)
	Proliferation	Yes	Direct	Ote et al. (2016)
Other	Aging	Yes	Direct	Han et al. (2017)
	Asexuality	Yes	Direct	Weiland-Bräuer et al. (2020)
	Life-history transitions	Yes	Unknown	Carrier et al. (2021)
	Phenotypic plasticity	Yes	Unknown	Carrier and Reitzel (2018)
	Pigmentation	Yes	Direct	Tsuchida et al. (2010)
	Regeneration	Yes	Unknown	Wang et al. (2021)
	Sex determination	Yes	Direct	Leclercq et al. (2016)

N.A., not applicable.

may be that more diverse neuronal and/or behavioral developmental processes are the partial result of partnerships with microbes residing on and in host tissues (Archie and Theis, 2011).

Conclusion: differentiation between development and symbiosis

Microbes influence diverse processes that are central to animal development and they use a myriad of mechanisms in these inter-kingdom interactions. This spectrum of influence spans much of developmental biology (Gilbert, 2001; Gilbert et al., 2015, 1996) and can be coarsely divided into five categories (gametogenesis, embryogenesis, cellular activity, differentiation and 'other'), with each having several related processes (30 in total). Microbes are currently known to be directly or indirectly involved in 70% of these and are hypothesized to be involved with many others (Table 1). Moreover, it has yet to be investigated or identified whether microbial cells are involved in 20% of these developmental processes and it is speculated that they are unlikely to be involved in another (Table 1).

Developmental processes that are exclusive to the animal host and those that are performed in concert with microbial symbionts are increasingly difficult to differentiate. We therefore find it appropriate to ask not whether microbes are involved in development, but which processes for a given species and its life-history strategies that these partnerships are necessary, or even essential, for and which mechanisms underlie these developmental symbioses. Moreover, the majority of core developmental processes that are now recognized to be linked to microbes were only identified in the last few years (Table 1). It is therefore possible or even likely that other fundamental developmental processes function as a partnership with microbial symbionts. One example may be fertilization and the polyspermy block. If symbiont fitness depends on preventing a hybridization between two emerging species, then mechanisms to inhibit fertilization and deter a polyspermy block when the sperm from the 'wrong' species wins the race to the egg could be possible (Brucker and Bordenstein, 2013; Carrier et al., 2021; Engelstädter and Hurst, 2009).

A fundamental paradigm shift and a new era is emerging in the way that we think about animal development. This Review underscores the elemental role of these inter-kingdom collaborations. As a result, our centuries-old host-centric view will inevitably fade, and development as the interplay between an animal host and a multitude of microbial prokaryotes will emerge as the rule (Bosch and McFall-Ngai, 2021; Gilbert, 2016; Gilbert et al., 2012). The magnitude of this conceptual shift has the potential to match that of the integration of evolutionary and ecological principles in embryology (Gilbert, 2001; Gilbert and Hadfield, 2022; Gilbert et al., 1996). This is largely because the central tenet of developmental symbiosis remains the same: to understand how these interactions influence the phenotype.

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Competing interests

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References

Apprill, A., Marlow, H., Martindale, M. and Rappé, M. (2009). The onset of microbial associations in the coral *Pocillopora meandrina*. *ISME J.* **3**, 685-699. doi:10.1038/ismej.2009.3

Archie, E. and Theis, K. (2011). Animal behaviour meets microbial ecology. *Anim. Behav.* **82**, 425-436. doi:10.1016/j.anbehav.2011.05.029

Arfken, A., Song, B., Allen, S., Jr. and Carnegie, R. (2021). Comparing larval microbiomes of the eastern oyster (*Crassostrea virginica*) raised in different hatcheries. *Aquaculture* **531**, 735955. doi:10.1016/j.aquaculture.2020.735955

Azam, F. and Malfatti, F. (2007). Microbial structuring of marine ecosystems. *Nat. Rev. Microbiol.* **5**, 782-791. doi:10.1038/nrmicro1747

Balbi, T., Vezzulli, L., Lasa, A., Pallavicini, A. and Canesi, L. (2020). Insight into the microbial communities associated with first larval stages of *Mytilus galloprovincialis*: possible interference by estrogenic compounds. *Comp. Biochem. Physiol. Part C Toxicol. Pharmacol.* **237**, 108833. doi:10.1016/j.cbpc.2020.108833

Bates, J., Mittge, E., Kuhlman, J., Baden, K., Cheesman, S. and Guillemin, K. (2006). Distinct signals from the microbiota promote different aspects of zebrafish gut differentiation. *Dev. Biol.* **297**, 374-386. doi:10.1016/j.ydbio.2006.05.006

Bishop, C., Jurga, E. and Graham, L. (2021). Patterns of bacterial diversity in embryonic capsules of the spotted salamander *Ambystoma maculatum*: an expanding view of a symbiosis. *FEMS Microbiol. Ecol.* **97**, fiab128. doi:10.1093/femsec/fiab128

Bordenstein, S. and Theis, K. (2015). Host biology in light of the microbiome: ten principles of holobionts and hologenomes. *PLoS Biol.* **13**, e1002226. doi:10.1371/journal.pbio.1002226

Bosch, T. (2014). Rethinking the role of immunity: lessons from *Hydra*. *Trends Immunol.* **35**, 495-502. doi:10.1016/j.it.2014.07.008

Bosch, T. and McFall-Ngai, M. (2021). Animal development in the microbial world: re-thinking the conceptual framework. *Curr. Top. Dev. Biol.* **141**, 399-427. doi:10.1016/bs.ctdb.2020.11.007

Bright, M. and Bulgheresi, S. (2010). A complex journey: transmission of microbial symbionts. *Nat. Rev. Microbiol.* **8**, 218-230. doi:10.1038/nrmicro2262

Brockes, J. and Kumar, A. (2008). Comparative aspects of animal regeneration. *Annu. Rev. Cell Dev. Biol.* **24**, 525-549. doi:10.1146/annurev.cellbio.24.110707.175336

Brooks, A., Kohl, K., Brucker, R., van Opstal, E. and Bordenstein, S. (2016). Phylosymbiosis: relationships and functional effects of microbial communities across host evolutionary history. *PLoS Biol.* **14**, e2000225. doi:10.1371/journal.pbio.2000225

Brough, C. and Dixon, A. (1990). Ultrastructural features of egg development in oviparae of the vetch aphid, *Megoura viciae* buckton. *Tissue Cell* **22**, 51-63. doi:10.1016/0040-8166(90)90089-R

Brucker, R. M. and Bordenstein, S. R. (2013). The hologenomic basis of speciation: gut bacteria cause hybrid lethality in the genus *Nasonia*. *Science* **341**, 667-669. doi:10.1126/science.1240659

Buchon, N., Broderick, N., Poidevin, M., Chakrabarti, S. and Lemaitre, B. (2009). Invasive and indigenous microbiota impact intestinal stem cell activity through multiple pathways in *Drosophila*. *Genes Dev.* **23**, 2333-2344. doi:10.1101/gad.1827009

Byrd, A., Belkaid, Y. and Segre, J. (2018). The human skin microbiome. *Nat. Rev. Microbiol.* **16**, 143-155. doi:10.1038/nrmicro.2017.157

Carrier, T. and Reitzel, A. (2017). The hologenome across environments and the implications of a host-associated microbial repertoire. *Front. Microbiol.* **8**, 802. doi:10.3389/fmicb.2017.00802

Carrier, T. and Reitzel, A. (2018). Convergent shifts in host-associated microbial communities across environmentally elicited phenotypes. *Nat. Commun.* **9**, 952. doi:10.1038/s41467-018-03383-w

Carrier, T. and Reitzel, A. (2019a). Bacterial community dynamics during embryonic and larval development of three confamilial echinoids. *Mar. Ecol. Prog. Ser.* **611**, 179-188. doi:10.3354/meps12872

Carrier, T. and Reitzel, A. (2019b). Shift in bacterial taxa precedes morphological plasticity in a larval echinoid. *Mar. Biol.* **166**, 164. doi:10.1007/s00227-019-3613-2

Carrier, T., Leigh, B., Deaker, D., Devens, H., Wray, G., Bordenstein, S., Byrne, M. and Reitzel, A. (2021). Microbiome reduction and endosymbiont gain from a switch in sea urchin life-history. *Proc. Natl. Acad. Sci. USA* **118**, e2022023118. doi:10.1073/pnas.2022023118

Carrier, T., Maldonado, M., Schmittmann, L., Pita, L., Bosch, T. and Hentschel, U. (2022). Symbiont transmission in marine sponges: reproduction, development, and metamorphosis. *BMC Biol.* **20**, 100. doi:10.1186/s12915-022-01291-6

Cary, S. and Giovannoni, S. (1993). Transovarial inheritance of endosymbiotic bacteria in clams inhabiting deep-sea hydrothermal vents and cold seeps. *Proc. Natl. Aced. Sci. USA* **90**, 5695-5699. doi:10.1073/pnas.90.12.5695
Cavalcanti, G., Alker, A., Delherbe, N., Malter, K. and Shikuma, N. (2020). The influence of bacteria on animal metamorphosis. *Annu. Rev. Microbiol.* **74**, 137-158. doi:10.1146/annurev-micro-011320-012753
Charbonneau, M., Blanton, L., DiGiulio, D., Relman, D., Lebrilla, C., Mills, D. and Gordon, J. (2016). A microbial perspective of human developmental biology. *Nature* **535**, 48-55. doi:10.1038/nature18845
Cheesman, S., Neal, J., Mittge, E., Seredick, B. and Guillemin, K. (2011). Epithelial cell proliferation in the developing zebrafish intestine is regulated by the Wnt pathway and microbial signaling via Myd88. *Proc. Natl. Acad. Sci. USA* **108**, 4570-4577. doi:10.1073/pnas.1000072107
Chung, H., Pamp, S., Hill, J., Surana, N., Edelman, S., Troy, E., Reading, N., Villablanca, E., Wang, S., Mora, J. et al. (2012). Gut immune maturation depends on colonization with a host-specific microbiota. *Cell* **149**, 1578-1593. doi:10.1016/j.cell.2012.04.037
Comizzoli, P., Power, M., Bornbusch, S. and Muletz-Wolz, C. (2021). Interactions between reproductive biology and microbiomes in wild animal species. *Anim. Microbiome* **3**, 87. doi:10.1186/s42523-021-00156-7
Coon, K., Vogel, K., Brown, M. and Strand, M. (2014). Mosquitoes rely on their gut microbiota for development. *Mol. Ecol.* **23**, 2727-2739. doi:10.1111/mec.12771
Cryan, J., O'Riordan, K., Cowan, C., Sandhu, K., Bastiaanssen, H., Boehme, M., Codagnone, M., Cussotto, S., Fulling, H., Golubeva, A. et al. (2019). The microbiota-gut-brain axis. *Physiol. Rev.* **99**, 1877-2013. doi:10.1152/physrev.00018.2018
Davidson, E. and Erwin, D. (2006). Gene regulatory networks and the evolution of animal body plans. *Science* **311**, 796-800. doi:10.1126/science.1113832
Davidson, S. and Stahl, D. (2008). Selective recruitment of bacteria during embryogenesis of an earthworm. *ISME J.* **2**, 510-518. doi:10.1038/ismej.2008.16
de Agüero, G., Ganal-Vonarburg, M., Fuhrer, S., Rupp, T., Uchimura, S., Li, Y., Steinert, H., Heikenwalder, A., Hapfelmeier, M., Sauer, S. et al. (2016). The maternal microbiota drives early postnatal innate immune development. *Science* **351**, 1296-1302. doi:10.1126/science.aad2571
Dedeine, F., Vavre, F., Fleury, F., Loppin, B., Hochberg, M. and Boulétreau, M. (2001). Removing symbiotic *Wolbachia* bacteria specifically inhibits oogenesis in a parasitic wasp. *Proc. Natl. Acad. Sci. USA* **98**, 6247-6252. doi:10.1073/pnas.101304298
Dedeine, F., Boulétreau, M. and Vavre, F. (2005). *Wolbachia* requirement for oogenesis: occurrence within the genus *Asobara* (Hymenoptera, Braconidae) and evidence for intraspecific variation in *A. tabida*. *Heredity* **95**, 394-400. doi:10.1038/sj.hdy.6800739
Díaz-Díaz, L., Rodríguez-Villafañe, A. and García-Arrarás, J. (2022). The role of the microbiota in regeneration-associated processes. *Front. Cell Dev. Biol.* **9**, 768783. doi:10.3389/fcell.2021.768783
Dittmer, J. and Brucker, R. (2021). When your host shuts down: larval diapause impacts host-microbiome interactions in *Nasonia vitripennis*. *Microbiome* **9**, 85. doi:10.1186/s40168-021-01037-6
Dougherty, M., Kudin, O., Mühlbauer, M., Neu, J., Gharaibeh, R. and Jobin, C. (2020). Gut microbiota maturation during early human life induces enterocyte proliferation via microbial metabolites. *BMC Microbiol.* **20**, 205. doi:10.1186/s12866-020-01892-7
Douglas, A. (1996). Reproductive failure and the free amino acid pools in pea aphids (*Acyrthosiphon pisum*) lacking symbiotic bacteria. *J. Insect Physiol.* **42**, 247-255. doi:10.1016/0022-1910(95)00105-0
Dubilier, N., Bergin, C. and Lott, C. (2008). Symbiotic diversity in marine animals: the art of harnessing chemosynthesis. *Nat. Rev. Microbiol.* **6**, 725-740. doi:10.1038/nrmicro1992
Dunn, C., Hejnol, A., Matus, D., Pang, K., Browne, W., Smith, S., Seaver, E., Rouse, G., Obst, M., Edgecombe, G. et al. (2008). Broad phylogenomic sampling improves resolution of the animal tree of life. *Nature* **452**, 745-749. doi:10.1038/nature06614
Eckelbarger, K. and Hodgson, A. (2021). Invertebrate oogenesis – a review and synthesis: comparative ovarian morphology, accessory cell function and the origins of yolk precursors. *Invertebr. Reprod. Dev.* **65**, 71-140. doi:10.1080/07924259.2021.1927861
Eisthen, H. and Theis, K. (2016). Animal–microbe interactions and the evolution of nervous systems. *Philos. Trans. R. Soc. B Biol. Sci.* **371**, 20150052. doi:10.1098/rstb.2015.0052
Engelstädter, J. and Hurst, G. (2009). The ecology and evolution of microbes that manipulate host reproduction. *Annu. Rev. Ecol. Evol. Syst.* **40**, 127-149. doi:10.1146/annurev.ecolsys.110308.120206
Ericson, C., Eisenstein, F., Medeiros, J., Malter, K., Cavalcanti, G., Zeller, R., Newman, D., Pilhofer, M. and Shikuma, N. (2019). A contractile injection system stimulates tubeworm metamorphosis by translocating a proteinaceous effector. *Elife* **8**, e46845. doi:10.7554/eLife.46845
Ezenwa, V., Gerardo, N., Inouye, D., Medina, M. and Xavier, J. (2012). Animal behavior and the microbiome. *Science* **338**, 198-199. doi:10.1126/science.1227412
Fast, E., Toomey, M., Panaram, K., Desjardins, D., Kolaczyk, E. and Frydman, H. (2011). *Wolbachia* enhance *Drosophila* stem cell proliferation and target the germline stem cell niche. *Science* **334**, 990-992. doi:10.1126/science.1209609
Ferree, P., Frydman, H., Li, J., Cao, J., Wieschaus, E. and Sullivan, W. (2005). *Wolbachia* utilizes host microtubules and dynein for anterior localization in the *Drosophila* oocyte. *PLoS Pathog.* **1**, e14. doi:10.1371/journal.ppat.0010014
Fieth, R. A., Gauthier, M.-E. A., Bayes, J., Green, K. M. and Degnan, S. M. (2016). Ontogenetic changes in the bacterial symbiont community of the tropical demosponge *Amphimedon queenslandica*: metamorphosis is a new beginning. *Front. Mar. Sci.* **3**, 228. doi:10.3389/fmars.2016.00228
Flórez, L. and Kaltenpoth, M. (2017). Symbiont dynamics and strain diversity in the defensive mutualism between *Lagria* beetles and *Burkholderia*. *Environ. Microbiol.* **19**, 3674-3688. doi:10.1111/1462-2920.13868
Foster, J., Rinaman, L. and Cryan, J. (2017). Stress & the gut-brain axis: regulation by the microbiome. *Neurobiol. Stress* **7**, 124-136. doi:10.1016/j.ynstr.2017.03.001
Foutaine, S. S., Mineo, P. and Kohl, K. (2022). Experimental manipulation of microbiota reduces host thermal tolerance and fitness under heat stress in a vertebrate ectotherm. *Nat. Ecol. Evol.* **6**, 405-417. doi:10.1038/s41559-022-01686-2
Franke, M., Geier, B., Hammel, J., Dubilier, N. and Leisch, N. (2021). Coming together—symbiont acquisition and early development in deep-sea bathymodioline mussels. *Proc. R. Soc. B* **288**, 20211044. doi:10.1098/rspb.2021.1044
Fraune, S. and Bosch, T. (2010). Why bacteria matter in animal development and evolution. *BioEssays* **32**, 571-580. doi:10.1002/bies.200900192
Fraune, S., Augustin, R., Anton-Erxleben, F., Wittlieb, J., Gelhaus, C., Klimovich, V., Samoilovich, M. and Bosch, T. (2010). In an early branching metazoan, bacterial colonization of the embryo is controlled by maternal antimicrobial peptides. *Proc. Natl. Acad. Sci. USA* **107**, 18067-18072. doi:10.1073/pnas.1008573107
Fraune, S., Anton-Erxleben, F., Augustin, R., Franzenburg, S., Knop, M., Schröder, K., Willoweit-Ohl, D. and Bosch, T. (2015). Bacteria–bacteria interactions within the microbiota of the ancestral metazoan *Hydra* contribute to fungal resistance. *ISME J.* **9**, 1543-1556. doi:10.1038/ismej.2014.239
Fronk, D. and Sachs, J. (2022). Symbiotic organs: the nexus of host–microbe evolution. *Trends Ecol. Evol.* **37**, 599-610. doi:10.1016/j.tree.2022.02.014
Gareau, M. (2014). Microbiota-gut-brain axis and cognitive function. In *Microbial Endocrinology: The Microbiota-Gut-Brain Axis in Health and Disease* (ed. M. Lyte and J. Cryan), pp. 357-371. SpringerLink.
Giere, O. and Langheld, C. (1987). Structural organisation, transfer and biological fate of endosymbiotic bacteria in gutless oligochaetes. *Mar. Biol.* **93**, 641-650. doi:10.1007/BF00392801
Giez, C., Klimovich, A. and Bosch, T. (2021). Neurons interact with the microbiome: an evolutionary-informed perspective. *Neuroforum* **27**, 89-98. doi:10.1515/nf-2021-0003
Gil-Turnes, M., Hay, M. and Fenical, W. (1989). Symbiotic marine bacteria chemically defend crustacean embryos from a pathogenic fungus. *Science* **246**, 116-118. doi:10.1126/science.2781297
Gilbert, S. (2001). Ecological developmental biology: developmental biology meets the real world. *Dev. Biol.* **233**, 1-12. doi:10.1006/dbio.2001.0210
Gilbert, S. (2016). Developmental plasticity and developmental symbiosis: the return of Evo-Devo. *Curr. Top. Dev. Biol.* **116**, 415-433. doi:10.1016/bs.ctdb.2015.12.006
Gilbert, S. and Hadfield, M. (2022). Symbiosis of disciplines: how can developmental biologists join conservationists in sustaining and restoring earth's biodiversity? *Development* **149**, dev199960. doi:10.1242/dev.199960
Gilbert, S., Opitz, J. and Raff, R. (1996). Resynthesizing evolutionary and developmental biology. *Dev. Biol.* **173**, 357-372. doi:10.1006/dbio.1996.0032
Gilbert, S. F., Sapp, J. and Tauber, A. I. (2012). A symbiotic view of life: we have never been individuals. *Q. Rev. Biol.* **87**, 325-341. doi:10.1086/668166
Gilbert, S., Bosch, T. and Ledón-Rettig, C. (2015). Eco-Evo-Devo: developmental symbiosis and developmental plasticity as evolutionary agents. *Nat. Rev. Genet.* **16**, 611-622. doi:10.1038/nrg3982
Gould, A., Zhang, V., Lamberti, L., Jones, E., Obadia, B., Korasidis, N., Gavryushkin, A., Carlson, J., Beerenwinkel, N. and Ludington, W. (2018). Microbiome interactions shape host fitness. *Proc. Natl. Acad. Sci. USA* **115**, E11951-E11960. doi:10.1073/pnas.180934911
Groussin, M., Mazel, F., Sanders, J., Smillie, C., Lavergne, S., Thuiller, W. and Alm, E. (2017). Unraveling the processes shaping mammalian gut microbiomes over evolutionary time. *Nat. Commun.* **8**, 14319. doi:10.1038/ncomms14319
Hadfield, M. (2011). Biofilms and marine invertebrate larvae: what bacteria produce that larvae use to choose settlement sites. *Ann. Rev. Mar. Sci.* **3**, 453-470. doi:10.1146/annurev-marine-120709-142753
Hammer, T. and Moran, N. (2019). Links between metamorphosis and symbiosis in holometabolous insects. *Philos. Trans. R. Soc. B* **374**, 20190068. doi:10.1098/rstb.2019.0068
Han, B., Sivaramakrishnan, P., Lin, C.-C. J., Neve, I. A. A., He, J., Tay, L. W. R., Sowa, J. N., Sizovs, A., Du, G., Wang, J. et al. (2017). Microbial genetic composition tunes host longevity. *Cell* **169**, 1249-1262.e13. doi:10.1016/j.cell.2017.05.036

Hansen, A. and Moran, N. (2012). Altered tRNA characteristics and 3' maturation in bacterial symbionts with reduced genomes. *Nucleic Acids Res.* **40**, 7870-7884. doi:10.1093/nar/gks503
Harumoto, T. and Lemaitre, B. (2018). Male-killing toxin in a bacterial symbiont of *Drosophila*. *Nature* **557**, 252-255. doi:10.1038/s41586-018-0086-2
Harumoto, T., Anbutsu, H., Lemaitre, B. and Fukatsu, T. (2016). Male-killing symbiont damages host's dosage-compensated sex chromosome to induce embryonic apoptosis. *Nat. Commun.* **7**, 12781. doi:10.1038/ncomms12781
Hentschel, U., Piel, J., Degnan, S. and Taylor, M. (2012). Genomic insights into the marine sponge microbiome. *Nat. Rev. Microbiol.* **10**, 641-654. doi:10.1038/nrmicro2839
Herren, J., Paredes, J., Schüpfer, F. and Lemaitre, B. (2013). Vertical transmission of a *Drosophila* endosymbiont via cooption of the yolk transport and internalization machinery. *mBio* **4**, e00532-512. doi:10.1128/mBio.00532-12
Hirose, E. (2015). Ascidian photosymbiosis: diversity of cyanobacterial transmission during tmbryogenesis. *Genesis* **53**, 121-131. doi:10.1002/dvg.22778
Horard, B., Terretaz, K., Gosselin-Grenet, A.-S., Sobry, H., Sicard, M., Landmann, F. and Loppin, B. (2022). Paternal transmission of the *Wolbachia* CidB toxin underlies cytoplasmic incompatibility. *Curr. Biol.* **32**, 1319-1331.e35. doi:10.1016/j.cub.2022.01.052
Ikuta, T., Igawa, K., Tame, A., Kuroiwa, T., Kuroiwa, H., Aoki, Y., Takaki, Y., Nagai, Y., Ozawa, G., Yamamoto, M. et al. (2016). Surfing the vegetal pole in a small population: extracellular vertical transmission of an 'intracellular' deep-sea clam symbiont. *R. Soc. Open Sci.* **3**, 160130. doi:10.1098/rsos.160130
Jäckle, O., Seah, B., Tietjen, M., Leisch, N., Liebeke, M., Kleiner, M., Berg, J. and Gruber-Vodicka, H. (2019). Chemosynthetic symbiont with a drastically reduced genome serves as primary energy storage in the marine flatworm *Paracatenula*. *Proc. Natl. Acad. Sci. USA* **116**, 8505-8514. doi:10.1073/pnas.1818995116
Kaiwa, N., Hosokawa, T., Nikoh, N., Tanahashi, M., Moriyama, M., Meng, X.-Y., Maeda, T., Yamaguchi, K., Shigenobu, S., Ito, M. et al. (2014). Symbiont-supplemented maternal investment underpinning host's ecological adaptation. *Curr. Biol.* **24**, 2465-2470. doi:10.1016/j.cub.2014.08.065
Kamada, N., Chen, G., Inohara, N. and Núñez, G. (2013). Control of pathogens and pathobionts by the gut microbiota. *Nat. Immuniol.* **14**, 685-690. doi:10.1038/ni.2608
Kaunitz, J. and Akiba, Y. (2019). Control of intestinal epithelial proliferation and differentiation: the microbiome, enteroendocrine L cells, telocytes, enteric nerves, and GLP, too. *Dig. Dis. Sci.* **64**, 2709-2716. doi:10.1007/s10620-019-05778-1
Kaur, R., Leigh, B., Ritchie, I. and Bordenstein, S. (2022). The cytoplasmic incompatibility Cif proteins from prophage WO modify sperm genome integrity. *PLoS Biol.* **20**, e3001584. doi:10.1371/journal.pbio.3001584
Kiefer, J., Batsukh, S., Bauer, E., Hirota, B., Weiss, B., Wierz, J., Fukatsu, T., Kaltenpoth, M. and Engl, T. (2021). Inhibition of a nutritional endosymbiont by glyphosate abolishes mutualistic benefit on cuticle synthesis in *Oryzaephilus surinamensis*. *Commun. Biol.* **4**, 554. doi:10.1038/s42003-021-02057-6
Kieft, T. and Simmons, K. (2015). Allometry of animal-microbe interactions and global census of animal-associated microbes. *Proc. R. Soc. B* **282**, 20150702. doi:10.1098/rspb.2015.0702
Klimovich, A. and Bosch, T. (2018). Rethinking the role of the nervous system: lessons from the *Hydra* holobiont. *BioEssays* **40**, 1800060. doi:10.1002/bies.201800060
Klimovich, A., Giacomello, S., Björklund, Å., Faure, L., Kaucka, M., Giez, C., Murillo-Rincon, A., Matt, A.-S., Willoweit-Ohl, D., Crupi, G. et al. (2020). Prototypical pacemaker neurons interact with the resident microbiota. *Proc. Natl. Acad. Sci. USA* **117**, 17854-17863. doi:10.1073/pnas.1920469117
Koenig, J., Spor, A., Scalfone, N., Fricker, A., Stombaugh, J., Knight, R., Angenent, L. and Ley, R. (2011). Succession of microbial consortia in the developing infant gut microbiome. *Proc. Natl. Acad. Sci. USA* **108**, 4578-4585. doi:10.1073/pnas.1000081107
Koga, R., Meng, X.-Y., Tsuchida, T. and Fukatsu, T. (2012). Cellular mechanism for selective vertical transmission of an obligate insect symbiont at the bacteriocyte–embryo interface. *Proc. Natl. Acad. Sci. USA* **109**, E1230-E1237. doi:10.1073/pnas.1119212109
Kohl, K. and Carey, H. (2016). A place for host-microbe symbiosis in the comparative physiologist's toolbox. *J. Exp. Biol.* **219**, 3496-3504. doi:10.1242/jeb.136325
Koren, O., Goodrich, J., Cullender, T., Spor, A., Laitinen, K., Bäckhed, H., Gonzalez, A., Werner, J., Angenent, L., Knight, R. et al. (2012). Host remodeling of the gut microbiome and metabolic changes during pregnancy. *Cell* **150**, 470-480. doi:10.1016/j.cell.2012.07.008
Kustra, M. and Carrier, T. (2022). On the spread of microbes that manipulate reproduction in marine invertebrates. *Am. Nat.*
Landmann, F., Foster, J., Slatko, B. and Sullivan, W. (2010). Asymmetric *Wolbachia* segregation during early *Brugia malayi* embryogenesis determines its distribution in adult host tissues. *PLoS Negl. Trop. Dis.* **4**, e758. doi:10.1371/journal.pntd.0000758
Landmann, F., Foster, J., Michalski, M., Slatko, B. and Sullivan, W. (2014). Co-evolution between an endosymbiont and Its nematode host: *Wolbachia* asymmetric posterior localization and AP polarity establishment. *PLoS Negl. Trop. Dis.* **8**, e3096. doi:10.1371/journal.pntd.0003096
Leclercq, S., Thézé, J., Chebbi, M., Giraud, I., Moumen, B., Ernenwein, L., Grève, P., Gilbert, C. and Cordaux, R. (2016). Birth of a W sex chromosome by horizontal transfer of *Wolbachia* bacterial symbiont genome. *Proc. Natl. Acad. Sci. USA* **113**, 15036-15041. doi:10.1073/pnas.1608979113
Lee, J., Park, K.-E., Lee, S., Jang, S., Eo, H. J., Am Jang, H., Kim, C.-H., Ohbayashi, T., Matsuura, Y., Kikuchi, Y. et al. (2017). Gut symbiotic bacteria stimulate insect growth and egg production by modulating hexamerin and vitellogenin gene expression. *Dev. Comp. Immunol.* **69**, 12-22. doi:10.1016/j.dci.2016.11.019
Lee, F., Williams, K., Levin, M. and Wolfe, B. (2018a). The bacterial metabolite indole inhibits regeneration of the planarian flatworm *Dugesia japonica*. *iScience* **10**, 135-148. doi:10.1016/j.isci.2018.11.021
Lee, Y.-S., Kim, T.-Y., Kim, Y., Lee, S.-H., Kim, S., Kang, S., Yang, J.-Y., Baek, I.-J., Sung, Y., Park, Y.-Y. et al. (2018b). Microbiota-derived lactate accelerates intestinal stem-cell-mediated epithelial development. *Cell Host Microbe* **24**, 833-846.e6. doi:10.1016/j.chom.2018.11.002
Levin, T. and King, N. (2013). Evidence for sex and recombination in the choanoflagellate *Salpingoeca rosetta*. *Curr. Biol.* **23**, 2176-2180. doi:10.1016/j.cub.2013.08.061
Li, Y.-F., Xu, J.-K., Chen, Y.-W., Ding, W.-Y., Shao, A.-Q., Liang, X., Zhu, Y.-T. and Yang, J.-L. (2019). Characterization of gut microbiome in the mussel *Mytilus galloprovincialis* in response to thermal stress. *Front. Physiol.* **10**, 1086. doi:10.3389/fphys.2019.01086
Maldonado, M. (2007). Intergenerational transmission of symbiotic bacteria in oviparous and viviparous demosponges, with emphasis on intracytoplasmically-compartmented bacterial types. *J. Mar. Biol. Assoc. UK* **87**, 1701-1713. doi:10.1017/S0025315407058080
Malter, K., Esmerode, M., Damba, M., Alker, A., Forsberg, E. and Shikuma, N. (2022). Diacylglycerol, PKC and MAPK signaling initiate tubeworm metamorphosis in response to bacteria. *Dev. Biol.* **487**, 99-109. doi:10.1016/j.ydbio.2022.04.009
Martin, J., Chong, T. and Ferree, P. (2013). Male killing *Spiroplasma* preferentially disrupts neural development in the *Drosophila melanogaster* embryo. *PLoS One* **8**, e79368. doi:10.1371/journal.pone.0079368
McCutcheon, J. and Moran, N. (2012). Extreme genome reduction in symbiotic bacteria. *Nat. Rev. Microbiol.* **10**, 13-26. doi:10.1038/nrmicro2670
McFall-Ngai, M. (2002). Unseen forces: the influence of bacteria on animal development. *Dev. Biol.* **242**, 1-14. doi:10.1006/dbio.2001.0522
McFall-Ngai, M. (2007). Care for the community. *Nature* **445**, 153-153. doi:10.1038/445153a
McFall-Ngai, M. (2014). The importance of microbes in animal development: lessons from the squid-*Vibrio* symbiosis. *Annu. Rev. Microbiol.* **68**, 177-194. doi:10.1146/annurev-micro-091313-103654
McFall-Ngai, M. and Ruby, E. (1991). Symbiont recognition and subsequent morphogenesis as early events in an animal-bacterial mutualism. *Science* **254**, 1491-1494. doi:10.1126/science.1962208
McFall-Ngai, M., Hadfield, M., Bosch, T., Carey, H., Domazet-Loso, T., Douglas, A., Dubilier, N., Eberl, G., Fukami, T., Gilbert, S. et al. (2013). Animals in a bacterial world, a new imperative for the life sciences. *Proc. Natl. Acad. Sci. USA* **110**, 3229-3236. doi:10.1073/pnas.1218525110
Metcalf, J., Henry, L., Rebolleda-Gómez, M. and Koskella, B. (2019). Why evolve reliance on the microbiome for timing of ontogeny? *mBio* **10**, e01496-19. doi:10.1128/mBio.01496-19
Moran, N., McCutcheon, J. and Nakabachi, A. (2008). Genomics and evolution of heritable bacterial symbionts. *Annu. Rev. Genet.* **42**, 165-190. doi:10.1146/annurev.genet.41.110306.130119
Moriano-Gutierrez, S., Bongrand, C., Essock-Burns, T., Wu, L., McFall-Ngai, M. and Ruby, E. (2020). The noncoding small RNA SsrA is released by *Vibrio fischeri* and modulates critical host responses. *PLoS Biol.* **18**, e3000934. doi:10.1371/journal.pbio.3000934
Mortzfeld, B., Urbanski, S., Reitzel, A., Künzel, S., Technau, U. and Fraune, S. (2015). Response of bacterial colonization in *Nematostella vectensis* to development, environment and biogeography. *Environ. Microbiol.* **18**, 1764-1781. doi:10.1111/1462-2920.12926
Murillo-Rincon, A., Klimovich, A., Pemöller, E., Taubenheim, J., Mortzfeld, B., Augustin, R. and Bosch, T. (2017). Spontaneous body contractions are modulated by the microbiome of *Hydra*. *Sci. Rep.* **7**, 15937. doi:10.1038/s41598-017-16191-x
Nowacki, M. (1993). Cell proliferation in colonic crypts of germ-free and conventional mice–preliminary report. *Folia Histochem. Cytobiol.* **31**, 77-81.
Nussbaumer, A., Fisher, C. and Bright, M. (2006). Horizontal endosymbiont transmission in hydrothermal vent tubeworms. *Nature* **441**, 345-348. doi:10.1038/nature04793
Nyholm, S. (2020). In the beginning: egg–microbe interactions and consequences for animal hosts. *Philos. Trans. R. Soc. B* **375**, 20190593. doi:10.1098/rstb.2019.0593
Nyholm, S. and Mcfall-Ngai, M. (2004). The winnowing: establishing the squid-*Vibrio* symbiosis. *Nat. Rev. Microbiol.* **2**, 632-642. doi:10.1038/nrmicro957

Nyholm, S. and McFall-Ngai, M. (2014). Animal development in a microbial world. In *Towards a Theory of Development* (ed. A. Minelli and T. Pradeu), pp. 260-273. Oxford University Press.
Nyholm, S. and McFall-Ngai, M. (2021). A lasting symbiosis: how the Hawaiian bobtail squid finds and keeps its bioluminescent bacterial partner. *Nat. Rev. Microbiol.* **19**, 666-679. doi:10.1038/s41579-021-00567-y
Oishi, S., Moriyama, M., Koga, R. and Fukatsu, T. (2019). Morphogenesis and development of midgut symbiotic organ of the stinkbug *Plautia stali* (Hemiptera: Pentatomidae). *Zool. Lett.* **5**, 16. doi:10.1186/s40851-019-0134-2
Ote, M., Ueyama, M. and Yamamoto, D. (2016). *Wolbachia* protein TomO targets nanos mRNA and restores germ stem cells in *Drosophila* sex-lethal mutants. *Curr. Biol.* **26**, 2223-2232. doi:10.1016/j.cub.2016.06.054
Pan, W., Sommer, F., Falk-Paulsen, M., Ulas, T., Best, P., Fazio, A., Kachroo, P., Luzius, A., Jentzsch, M., Rehman, A. et al. (2018). Exposure to the gut microbiota drives distinct methylome and transcriptome changes in intestinal epithelial cells during postnatal development. *Genome Med.* **10**, 27. doi:10.1186/s13073-018-0534-5
Pannebakker, B., Loppin, B., Elemans, C., Humblot, L. and Vavre, F. (2007). Parasitic inhibition of cell death facilitates symbiosis. *Proc. Natl. Acad. Sci. USA* **104**, 213-215. doi:10.1073/pnas.0607845104
Purcell, E. (1977). Life at low Reynolds number. *Am. J. Phys.* **45**, 3-11. doi:10.1119/1.10903
Rabatel, A., Febvay, G., Gaget, K., Duport, G., Baa-Puyoulet, P., Sapountzis, P., Bendridi, N., Rey, M., Rahbé, Y., Charles, H. et al. (2013). Tyrosine pathway regulation is host-mediated in the pea aphid symbiosis during late embryonic and early larval development. *BMC Genom.* **14**, 235. doi:10.1186/1471-2164-14-235
Rawls, J. F., Samuel, B. S. and Gordon, J. I. (2004). Gnotobiotic zebrafish reveal evolutionarily conserved responses to the gut microbiota. *Proc. Natl. Acad. Sci. USA* **101**, 4596-4601. doi:10.1073/pnas.0400706101
Reedy, A., Luo, L., Neish, A. and Jones, R. (2019). Commensal microbiota-induced redox signaling activates proliferative signals in the intestinal stem cell microenvironment. *Development* **146**, dev171520. doi:10.1242/dev.171520
Reshef, L., Koren, O., Loya, Y., Zilber-Rosenberg, I. and Rosenberg, E. (2006). The coral probiotic hypothesis. *Environ. Microbiol.* **8**, 2068-2073. doi:10.1111/j.1462-2920.2006.01148.x
Rewitz, K., Yamanaka, N., Gilbert, L. and O'Conner, M. B. (2009). The insect neuropeptide PTTH activates teceptor tyrosine kinase torso to initiate metamorphosis. *Science* **326**, 1403-1405. doi:10.1126/science.1176450
Riesgo, A., Maldonado, M. and Durfort, M. (2007). Dynamics of gametogenesis, embryogenesis, and larval release in a Mediterranean homosclerophorid demosponge. *Mar. Freshw. Res.* **58**, 398-417. doi:10.1071/MF06052
Round, J. and Mazmanian, S. (2009). The gut microbiome shapes intestinal immune responses during health and disease. *Nat. Rev. Immunol.* **9**, 313-323. doi:10.1038/nri2515
Rowe, M., Veerus, L., Trosvik, P., Buckling, A. and Pizzari, T. (2020). The reproductive microbiome: an emerging driver of sexual selection, sexual conflict, mating systems, and reproductive isolation. *Trends Ecol. Evol.* **35**, 220-234. doi:10.1016/j.tree.2019.11.004
Russell, S. (2019). Transmission mode is associated with environment type and taxa across bacteria-eukaryote symbioses: a systematic review and meta-analysis. *FEMS Microbiol. Lett.* **366**, fnz013. doi:10.1093/femsle/fnz013
Russell, S. and Castillo, J. (2020). Trends in symbiont-induced host cellular differentiation. In *Symbiosis: Cellular, Molecular, Medical, and Evolutionary Aspects* (ed. M. Kloc), pp. 137-176. Springer.
Russell, S., Lemseffer, N. and Sullivan, W. (2018). Wolbachia and host germline components compete for kinesin-mediated transport to the posterior pole of the Drosophila oocyte. *PLoS Pathog.* **14**, e1007216. doi:10.1371/journal.ppat.1007216
Sandall, J., Tribe, R., Avery, L., Mola, G., Visser, G., Homer, C., Gibbons, D., Kelly, N., Kennedy, H., Kidanto, H. et al. (2018). Short-term and long-term effects of caesarean section on the health of women and children. *Lancet* **392**, 1349-1357. doi:10.1016/S0140-6736(18)31930-5
Schuh, N., Carrier, T., Schrankel, C., Reitzel, A., Heyland, A. and Rast, J. (2020). Bacterial exposure mediates developmental plasticity and resistance of lethal *Vibrio lentus* infection in purple sea urchin (*Strongylocentrotus purpuratus*) larvae. *Front. Immunol.* **10**, 3014. doi:10.3389/fimmu.2019.03014
Sender, R., Fuchs, S. and Milo, R. (2016). Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol.* **14**, e1002533. doi:10.1371/journal.pbio.1002533
Serbus, L. and Sullivan, W. (2007). A cellular basis for *Wolbachia* recruitment to the host germline. *PLoS Pathog.* **3**, e190. doi:10.1371/journal.ppat.0030190
Sharon, G., Sampson, T., Geschwind, D. and Mazmanian, S. (2016). The central nervous system and the gut microbiome. *Cell* **167**, 915-932. doi:10.1016/j.cell.2016.10.027
Sharp, K., Davidson, S. and Haygood, M. (2007). Localization of 'Candidatus *Endobugula sertula*' and the bryostatins throughout the life cycle of the bryozoan *Bugula neritina*. *ISME J.* **1**, 693-702. doi:10.1038/ismej.2007.78
Shikuma, N., Pilhofer, M., Weiss, G., Hadfield, M., Jensen, G. and Newman, D. (2014). Marine tubeworm metamorphosis induced by arrays of bacterial phage tail-like structures. *Science* **343**, 529-533. doi:10.1126/science.1246794
Sison-Mangus, M., Mushegian, A. and Ebert, D. (2015). Water fleas require microbiota for survival, growth, and reproduction. *ISME J.* **9**, 59-67. doi:10.1038/ismej.2014.116
Solis, A., Klapholz, M., Zhao, J. and Levy, M. (2020). The bidirectional nature of microbiome-epithelial cell interactions. *Curr. Opin. Microbiol.* **56**, 45-51. doi:10.1016/j.mib.2020.06.007
Sommer, F. and Bäckhed, F. (2013). The gut microbiota — masters of host development and physiology. *Nat. Rev. Microbiol.* **11**, 227-238. doi:10.1038/nrmicro2974
Song, S., Sanders, J., Delsuc, F., Metcalf, J., Amato, K., Taylor, M., Mazel, F., Lutz, H., Winker, K., Graves, G. et al. (2020). Comparative analyses of vertebrate gut microbiomes reveal convergence between birds and bats. *mBio* **11**, e02901-ee02919. doi:10.1128/mBio.02901-19
Song, H., Hewitt, O. and Degnan, S. (2021). Arginine biosynthesis by a bacterial symbiont enables nitric oxide production and facilitates larval settlement in the marine-sponge host. *Curr. Biol.* **31**, 433-437.e3. doi:10.1016/j.cub.2020.10.051
Sonnenburg, E., Smits, S., Tikhonov, M., Higginbottom, S., Wingreen, N. and Sonnenburg, J. (2016). Diet-induced extinctions in the gut microbiota compound over generations. *Nature* **529**, 212-215. doi:10.1038/nature16504
Stephens, W., Burns, A., Stagaman, K., Wong, S., Rawls, J., Guillemin, K. and Bohannan, B. (2016). The composition of the zebrafish intestinal microbial community varies across development. *ISME J.* **10**, 644-654. doi:10.1038/ismej.2015.140
Stevens, L., Giordano, R. and Fialho, R. (2001). Male-killing, nematode infections, bacteriophage infection, and virulence of cytoplasmic bacteria in the genus *Wolbachia*. *Annu. Rev. Ecol. Syst.* **32**, 519-545. doi:10.1146/annurev.ecolsys.32.081501.114132
Strathmann, R. (1985). Feeding and nonfeeding larval development and life-history evolution in marine invertebrates. *Annu. Rev. Ecol. Syst.* **16**, 339-361. doi:10.1146/annurev.es.16.110185.002011
Strunov, A., Schmidt, K., Kapun, M. and Miller, W. (2022). Restriction of *Wolbachia* bacteria in early embryogenesis of neotropical *Drosophila* species via endoplasmic reticulum-mediated autophagy. *mBio.* **13**, e0386321. doi:10.1128/mbio.03863-21
Tanak, E. and Reddien, P. (2011). The cellular basis for animal regeneration. *Dev. Cell* **21**, 172-185. doi:10.1016/j.devcel.2011.06.016
Thaiss, C., Zmora, N., Levy, M. and Elinav, E. (2016). The microbiome and innate immunity. *Nature* **535**, 65-74. doi:10.1038/nature18847
Tomic–Canic, M., Burgess, J., O'Neill, K., Strbo, N. and Pastar, I. (2020). Skin microbiota and its interplay with wound healing. *Am. J. Clin. Dermatol.* **21**, 36-43. doi:10.1007/s40257-020-00536-w
Troll, J., Hamilton, M., Abel, M., Ganz, J., Bates, J., Stephens, Z., Melancon, E., van der Vaart, M., Meijer, A., Distel, M. et al. (2018). Microbiota promote secretory cell determination in the intestinal epithelium by modulating host Notch signaling. *Development* **145**, dev155317. doi:10.1242/dev.155317
Tsuchida, T., Koga, R., Horikawa, M., Tsunoda, T., Maoka, T., Matsumoto, S., Simon, J. and Fukatsu, T. (2010). Symbiotic bacterium modifies aphid body color. *Science* **330**, 1102-1104. doi:10.1126/science.1195463
Vicick, K. L., Stabb, E. V. and Ruby, E. G. (2021). A lasting symbiosis: how *Vibrio fischeri* finds a squid partner and persists within its natural host. *Nat. Rev. Microbiol.* **19**, 654-665. doi:10.1038/s41579-021-00557-0
Vijayan, N., Lema, K. A., Nedved, B. T. and Hadfield, M. G. (2019). Microbiomes of the polychaete *Hydroides elegans* (Polychaeta: Serpulidae) across its life-history stages. *Mar. Biol.* **166**, 19. doi:10.1007/s00227-019-3465-9
Vogel, S. (1994). *Life in Moving Fluids: The Physical Biology of Flow*. Priceton University Press.
Vuong, H., Pronovost, G., Williams, D., Coley, E., Siegler, E., Qiu, A., Kazantsev, M., Wilson, C., Rendon, T. and Hsiao, E. (2020). The maternal microbiome modulates fetal neurodevelopment in mice. *Nature* **586**, 281-286. doi:10.1038/s41586-020-2745-3
Waddington, C. (1956). *The Principles of Embryology*. London: Routledge.
Wang, G., Sweren, E., Liu, H., Wier, E., Alphonse, M., Chen, R., Islam, N., Li, A., Xue, Y., Chen, J. et al. (2021). Bacteria induce skin regeneration via IL-1β signaling. *Cell Host Microbe* **29**, 777-791.e6. doi:10.1016/j.chom.2021.03.003
Wei, G., Martin, K., Xing, P., Agrawal, R., Whiley, L., Wood, T., Hejndorf, S., Ng, Y., Low, J., Rossant, J. et al. (2021). Tryptophan-metabolizing gut microbes regulate adult neurogenesis via the aryl hydrocarbon receptor. *Proc. Natl. Acad. Sci. USA* **118**, e2021091118. doi:10.1073/pnas.2021091118
Weigel, B. (2020). Sea cucumber intestinal regeneration reveals deterministic assembly of the gut microbiome. *Appl. Environ. Microbiol.* **86**, e00489-e00420. doi:10.1128/AEM.00489-20
Weiland-Bräuer, N., Pinnow, N., Langfeldt, D., Roik, A., Güllert, S., Chibani, C., Reusch, T. and Schmitz, R. (2020). The native microbiome is crucial for offspring generation and fitness of *Aurelia aurita*. *mBio* **11**, e02336-20. doi:10.1128/mBio.02336-20
West-Eberhard, M. (2003). *Developmental Plasticity and Evolution*. Oxford, UK: Oxford University Pres.

Williams, K., Bischof, J., Lee, F., Miller, K., LaPalme, J., Wolfe, B. and Levin, M. (2020). Regulation of axial and head patterning during planarian regeneration by a commensal bacterium. *Mech. Dev.* **163**, 103614. doi:10.1016/j.mod.2020.103614

Woznica, A., Cantley, A., Beemelmanns, C., Freinkman, E., Clardy, J. and King, N. (2016). Bacterial lipids activate, synergize, and inhibit a developmental switch in choanoflagellates. *Proc. Natl. Acad. Sci. USA* **113**, 7894-7899. doi:10.1073/pnas.1605015113

Yatsunenko, T., Rey, F., Manary, M., Trehan, I., Dominguez-Bello, M., Contreras, M., Magris, M., Hidalgo, G., Baldassano, R., Anokhin, A. et al. (2012). Human gut microbiome viewed across age and geography. *Nature* **486**, 222-227. doi:10.1038/nature11053

Ye, L. and Rawls, J. (2021). Microbial influences on gut development and gut-brain communication. *Development* **148**, dev194936. doi:10.1242/dev.194936

Zegarra-Ruiz, D., Kim, D., Norwood, K., Kim, M., Wu, W., Saldana-Morales, F., Hill, A., Majumdar, S., Orozco, S., Bell, R. et al. (2021). Thymic development of gut-microbiota-specific T cells. *Nature* **594**, 413-417. doi:10.1038/s41586-021-03531-1

Zheng, D., Liwinski, T. and Elinav, E. (2020a). Interaction between microbiota and immunity in health and disease. *Cell Res.* **30**, 492-506. doi:10.1038/s41422-020-0332-7

Zheng, W., Zhao, W., Wu, M., Song, X., Caro, F., Sun, X., Gazzaniga, F., Stefanetti, G., Oh, S., Mekalanos, J. et al. (2020b). Microbiota-targeted maternal antibodies protect neonates from enteric infection. *Nature* **577**, 543-548. doi:10.1038/s41586-019-1898-4

Zhou, G., Cai, L., Yuan, T., Tian, R., Tong, H., Zhang, W., Jiang, L., Guo, M., Liu, S., Qian, P.-Y. et al. (2017). Microbiome dynamics in early life stages of the scleractinian coral *Acropora gemmifera* in response to elevated *p*CO2. *Environ. Microbiol.* **18**, 3342-3352. doi:10.1111/1462-2920.13840

Zilber-Rosenberg, I. and Rosenberg, E. (2008). Role of microorganisms in the evolution of animals and plants: the hologenome theory of evolution. *FEMS Microbiol. Rev.* **32**, 723-735. doi:10.1111/j.1574-6976.2008.00123.x