

## 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*

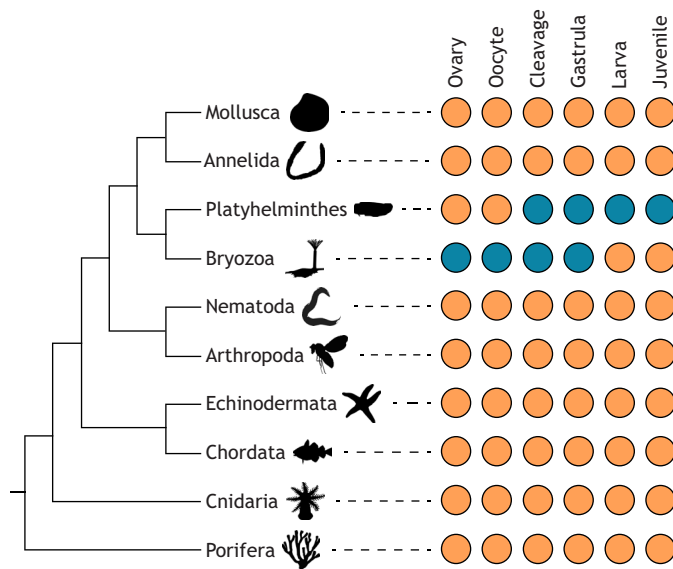
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**Fig. 1. Animal phylogeny and developmental symbiosis.** Microbial prokaryotes are present (orange circles) in the reproductive and developmental stages of all major animal lineages (i.e. the ten with the most known species; this does not include the early-diverging ctenophores, of which no studies were found), with Bryozoa and Platyhelminthes 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](http://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 Kaltentpoth, 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

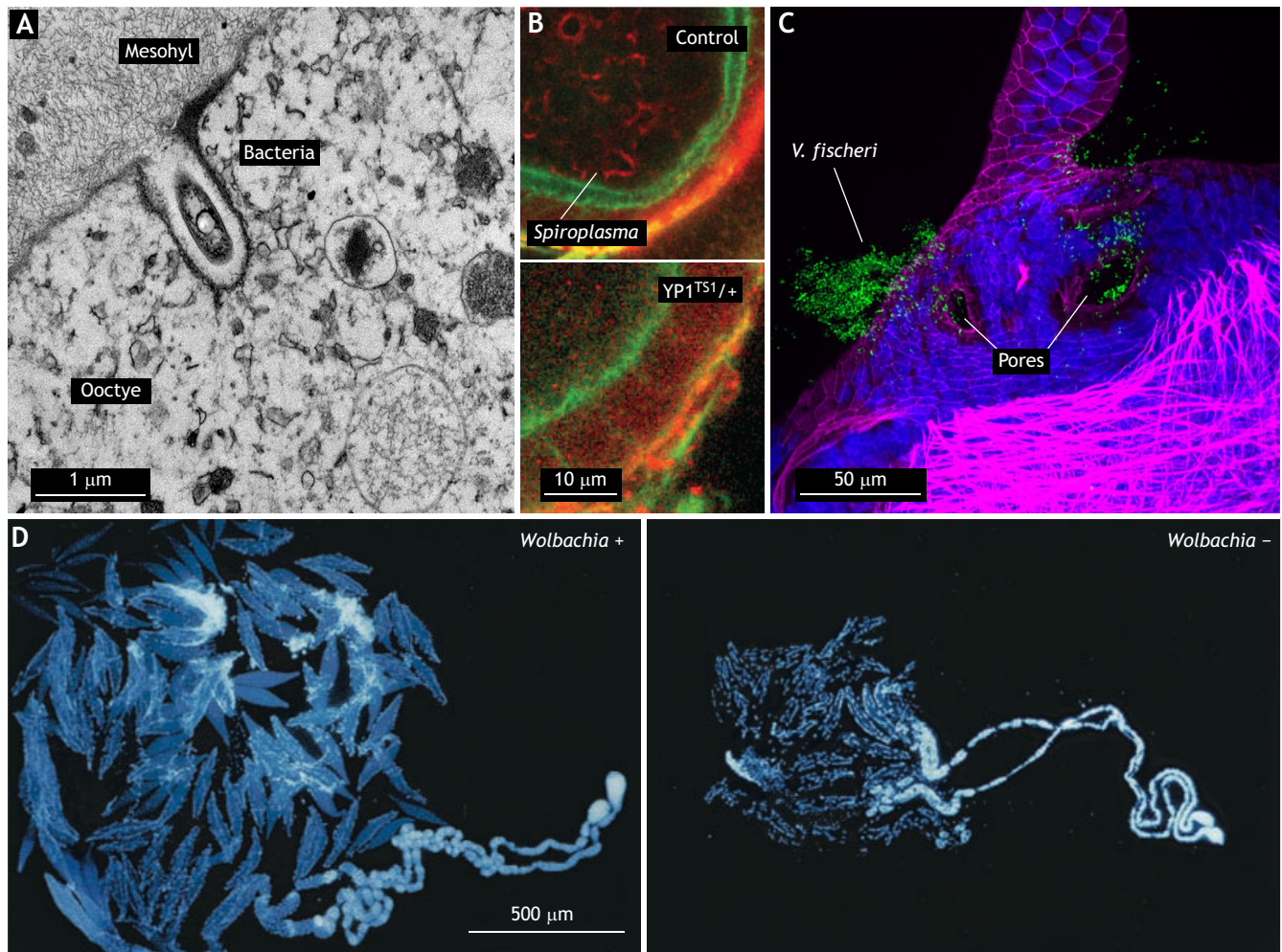
germ cells that later differentiate into the female germline (Ferree et al., 2005; Landmann et al., 2014, 2010; Russell et al., 2018; Serbus and Sullivan, 2007; Strunov et al., 2022). Once in the female germline, *Wolbachia* spp. cells can enhance the maintenance of germline stem cells by excreting proteins 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



**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<sup>TS1/+</sup>; 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* (Fontaine 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

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 elevated 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).

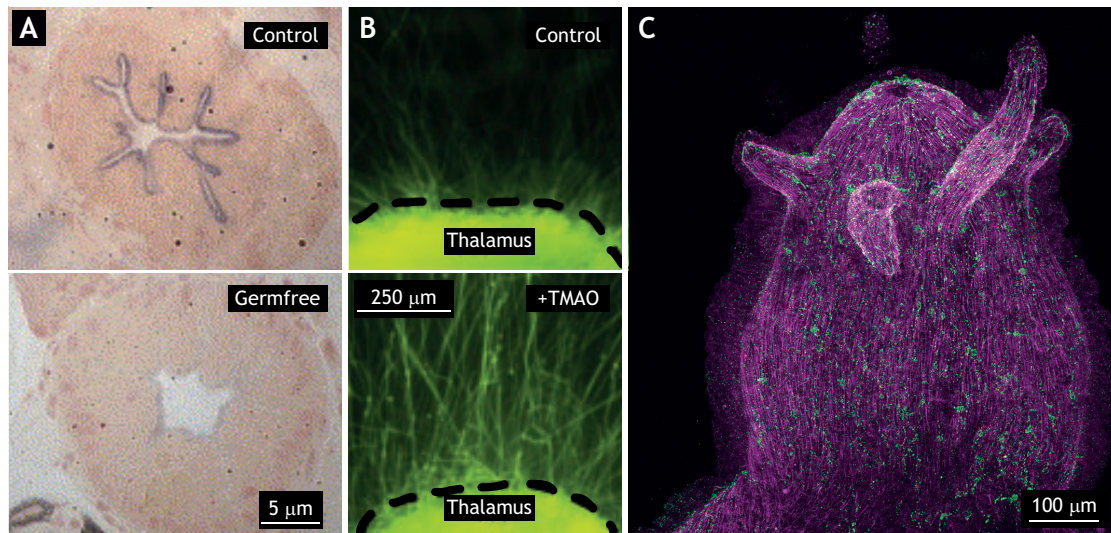
### Host-microbe interactions post-embryogenesis

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  $\gamma$ -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,



**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  $\beta$ -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; Yatsunencko 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).

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)
Cellular activity	Metamorphosis	Yes	Direct	Shikuma et al. (2014); Song et al. (2021)
	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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**Table S1.** A representative (but not compensative) list of references for each reproductive and developmental stage for the major animal phyla. This corresponds with Figure 1. Please note that “Ovary” is used as a general term to describe the host’s reproductive system and is not always used in a literal sense.

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