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27 Symbionts as an Epigenetic Source of Heritable Variation

Scott F. Gilbert

Evolution arises from heritable changes in development. Most evolutionary developmental biology has focused on changes in the regulatory components of the genome. However, development also includes interactions between organisms and their environments. One area of interest concerns the importance of symbionts for the production of the normal range of phenotypes. Many, if not most, organisms have “outsourced” some of their developmental signals to a set of symbionts that are expected to be acquired during development. Such intimate interactions between species are referred to as codevelopment, the production of a new individual through the coordinated interactions of several genotypically different species. Several research programs have demonstrated that such codevelopmental partnerships can be selected. Here I focus on symbioses in coral reef cnidarians and pea aphids, wherein the symbiotic system provides thermotolerance for the composite organism, and on mice, whose gut symbionts provide critical signals for host gut development, immune function, and fat storage.

The theory of evolution by natural selection is predicated on the existence of widespread variation within species. But from whence does this variation arise? Darwin (1859) realized that selection could not act upon characters that had not yet appeared, noting that “characters may have originated from quite secondary sources, independently from natural selection.” He continued this line of reasoning in his book *The Variation of Animals and Plants Under Domestication* (1868), in which he concludes (p. 351, in his discussion of the origin of nectarines from several different varieties of peach, each in a different environment), “the external conditions of life are quite insignificant, in relationship to any particular variation, in comparison with the organization and constitution of the being which varies. We are thus driven to conclude that in most cases the conditions of life play a subordinate part in causing any particular modification...” The sources of variation remained obscure.

Population genetics provided the first set of answers to Darwin’s quandary. Alleles of the protein-encoding regions of the genome were shown to be major

sources of variation. Later, allelic differences in the cis-regulatory regions provided developmental genetic mechanisms of variation (Arthur 2004; Gilbert and Epel 2009): heterochrony (change in the timing of gene expression), heterotopy (change in the cells in which genes are expressed), and heterometry (change in the amount of gene expression). Examples have been found for each of these mechanisms.

There are also environmentally induced components of developmental variation. These include developmental plasticity, developmental symbioses, and epialleles caused by environmentally induced chromatin modification. It is therefore important to determine if these environmental mechanisms produce selectable variation. The selectability of epialleles and developmental plasticity has been discussed by Jablonka and colleagues (Jablonka and Lamb 1995; Jablonka and Raz 2009) and by West-Eberhard (2003, 2005). Thus, in addition to genetic variation, there is also selectable epigenetic variation. This chapter will focus on one of those epigenetic inheritance systems, developmental symbiosis.

Developmental Partnerships

Darwin's idea of the "struggle for existence," in which competition exists between "one individual with another of the same species, or with the individuals of distinct species" (1859) sets up a framework in which each individual is essentially singular, competing only for itself and the survival and propagation of its lineage. But this situation changes if the "individual" is actually a "team" or a "consortium" of cells with different genotypes. Gilbert (2002) referred to this chimeric mode of development as "interspecies epigenesis," emphasizing the developmental roles played by symbionts and the notion that the fertilized egg is not an autopoietic, self-creating, entity. Rosenberg, Koren, Reshef, Efrony, and Zilber-Rosenberg (2007) referred to this phenomenon of variation through symbiosis as "the hologenome theory of evolution." They called the host and its full symbiont population the *holobiont*, and they named the combination of the host genome and the genomes of all its symbiotic organisms the *hologenome*. However, this original hologenome concept did not include development as an aspect, and I would like to expand it to include not only symbiosis but also *symbiopoiesis*—the codevelopment of the holobiont.

More and more, symbiosis appears to be the "rule," not the exception (McFall-Ngai 2002; Saffo 2006; Gilbert and Epel 2009). One well-studied example of developmental symbiosis is the colonies of the bacterium *Vibrio fischeri* residing within the mantle of the Hawaiian bobtail squid, *Euprymna scolopes*. *Euprymna* prey on shrimp in shallow water, but they run the risk of alerting predatory fish to their presence if the moon casts the squid's shadow onto the seafloor. The bobtail squid deals with this potential threat by emitting light from its underside, thereby hiding its shadow from potential predators. The squid does not accomplish this feat alone;

the presence of *Vibrio fischeri* in the squid's light organ is required to generate the squid's characteristic glow. Both the squid and the bacterium benefit from this mutualistic relationship. The squid gains protection from predators and the bacterium is able to live safely within the host's light organ, an environment free of predators and adverse environmental conditions. More significantly, *Vibrio fischeri* actually constructs the light organ in which it will reside. The newly hatched squid collects bacteria from the seawater. Only members of the species *V. fischeri* are allowed to adhere to the underside of the squid and to induce apoptosis in the tissue that will become the light organ. And only when they have reached a certain density do they begin to emit light (Nyholm and McFall-Ngai 2004; Visick and Ruby 2006).

The development of numerous insects involves obligate symbiosis with bacterial partners. Normal female development in the wasp *Asobara tabida* is dependent on *Wolbachia* infection. If *A. tabida* females are treated with antibiotics that kill their symbiotic bacteria, the ovaries of the female wasps undergo apoptosis, and eggs are not produced (Dedeine, Vavre, Fleury, Loppin, Hochberg, and Boulétreau 2001; Pannebakker, Loppin, Elemans, Humblot, and Vavre 2007). Unlike the squids, which receive their symbionts "horizontally" from the seawater, *A. tabida* infects its juveniles "vertically" through the egg cytoplasm. Thus, *Wolbachia* bacteria become an epigenetically transmitted source of critical developmental signals. Such essential developmental relationships are common throughout the animal kingdom, and they are well known throughout the plant kingdom (McFall-Ngai 2002; Gilbert and Epel 2009). An orchid may produce thousands of seeds, but these seeds have no carbon reserves. Only those seeds that find a fungal partner can get the carbon they need to germinate (Waterman and Bidartondo 2008). Symbiosis is a major player in the evolutionary game. It is not just for lichens.

The host and symbiont species interact in ways that are vital to the proper functioning of both organisms. Disruption of that interaction can lead to illness and death. For example, Mazmanian, Liu, Tzianabos, and Kasper (2005) showed that mice raised without gut microbiota have deficient proliferation of helper T cells, but the introduction of *Bacteroides fragilis* into the gut was enough to stimulate T cell expansion. They were also able to demonstrate that *B. fragilis* protects mice from experimental bowel colitis normally induced by a second symbiotic bacterium, *Helicobacter hepaticus* (Mazmanian, Round, and Kasper 2008). In exchange for these benefits, the mice provide the bacterium with a relatively safe and nutrient-rich environment. This has important medical implications for the health of humans, considering that the human digestive tract harbors over five hundred species of bacteria (Gilbert and Epel 2009).

These symbionts and hosts do not lead independent existences. Rather, each is the cause of the other's development. The *Bacteroides* in the mammalian gut induce the expression of genes in the intestinal epithelium, resulting in the proper develop-

ment of the mammalian gut, gut vasculature, and host immune system (Hooper, Wong, Thelin, Hansson, Falk, and Gordon 2001; Rhee, Sethupathi, Driks, Lanning, and Knight 2004). *Bacteroides*, for instance, induce gene expression in the intestinal Paneth cells to produce Angiogenin-4 and RegIII. These proteins provide benefits to both the mammalian body and the *Bacteroides*. Angiogenin-4 helps induce blood vessel development in the villi, and both Angiogenin-4 and RegIII are selective bacteriocidal proteins that kill competitors of *Bacteroides*, such as *Listeria*. (Hooper, Stappenbeck, Hong, and Gordon 2003; Cash, Whitman, Benedict, and Hooper 2006). In inducing gene expression in its host's intestinal epithelium, *Bacteroides* does well by doing good. It helps construct its own niche by creating mutually favorable conditions in the gut (see Laland, Odling-Smee, and Gilbert 2008). In return, human intestinal cells instruct the bacteria to produce biofilms, allowing the bacteria to continue residence therein. Thus, as expected in development, there are reciprocal inductions. Only here, they are between different species residing in the same body. Kauffman (1995) famously said that "All evolution is coevolution." The situation may actually be more intimate. Almost all development may be codevelopment. By "codevelopment" I refer to the ability of the cells of one species to assist the normal construction of the body of another species.

Codevelopment

It has been proposed that symbiotic relationships are unstable over evolutionary time, and thus are both rare and evolutionarily transient, because organisms with genotypes that confer advantages to non-kin are at a disadvantage in comparison with organisms with "selfish" genotypes that do not provide other species with such benefits (see Douglas 2007). However, the persistence of symbioses such as the coral-algae symbiosis that evolved about 240 million years ago and continues to this day, indicates otherwise. Most symbiotic relationships involve microorganisms that have fast growth rates and thus can change more rapidly under environmental stresses than invertebrates or vertebrates. Rosenberg, Koren, Reshef, Efrony, and Zilber-Rosenberg (2007) describe four mechanisms by which microorganisms may confer greater adaptive potential to the hologenome than the host genome can alone. First, the relative abundance of microorganisms associated with the host can be changed due to environmental pressure. Second, adaptive variation can result from the introduction of a new symbiont into the community. Third, changes to the microbial genome can occur through recombination or random mutation, and these changes can occur in a microbial symbiont more rapidly than in the host. Fourth, there is the possibility of horizontal gene transfer between members of the holobiont. This possibility was shown to be realized in the symbiosis of humans with different species of gut bacteria (Hehemann et al. 2010).

In a symbiotic relationship, the interactions among partners can affect the evolutionary fitness of both the symbiont and the host. While the genomes of the individual symbionts affect the development of each organism, development of symbiotic species is also regulated by interactions of the symbiont genomes within the holobiont (Gilbert and Epel 2009). This in turn can alter the fitness of the organisms involved in the symbiosis, which would make the symbiotic relationship an integrated evolutionary unit. In this sense, the individual is actually a community of organisms behaving as an ecosystem. In group selection theory, the group is usually treated as an individual. Here, the individual is treated as a group. Nature may be selecting “relationships” rather than individuals or genomes. What we usually consider to be an “individual” is often a multispecies group that is under selection.

If the relationship between symbiotic species is so important, then perhaps the environment selects not only on each species in the relationship but also among variants of the holobiont. The fitness traits would therefore be not merely those of the host but also the traits of the group per se. Therefore, it may prove useful to look at the evolution of a species in the context of the hologenome. This view of evolution would link these hosts and symbionts together as a single coevolving unit, because the fitness of each species would rely on its interactions with the other species in the symbiosis. The two cases presented in this chapter focus on the thermotolerance of hologenomes due to changes in one of the symbiont genomes in the symbiosis. These cases include corals with zooxanthellae and pea aphids with the bacteria *Buchnera aphidicola*.

Selectable Thermotolerance in the Coral and *Symbiodinium* Partnership

Symbiodinium is a genus of photosynthetic endosymbiotic dinoflagellates. The genus comprises multiple species of zooxanthella algae which have been found to inhabit the tissues of scleractinia (stony) coral. These coral are largely dependent on their endosymbionts for survival and in return provide the zooxanthella with protection, nutrients, and a supply of carbon dioxide for photosynthetic products. Under stressful environmental conditions, corals undergo a bleaching event in which they expel or digest their endosymbiont populations, leaving behind a white skeletal structure. Such events have increased in recent decades and are expected to occur more frequently in the near future due to global warming (Hoegh-Guldberg, Mumby, Hooten, Steneck, Greenfield, Gomez, Harvell et al. 2007).

Within the *Symbiodinium* genus there exists a great deal of genetic diversity, and six clades form symbiotic relationships with corals (Baker 2003; Pochon, Montoya-Burgos, Stadelman, and Pawlowski 2006). *Symbiodinium* clades can differ in traits such as thermal tolerance and the photosynthetic response to light (Robinson and Warner 2006). Clade D zooxanthellae, for instance, are less heat sensitive than Clade

C zooxanthellae and can tolerate higher temperatures (Fabricius, Mieog, Colin, Idip, and Van Oppen 2004). Genetically distinct coral colonies can have unique zooxanthellae DNA fingerprints (Goulet and Coffroth 2003), and real-time PCR methods that can detect background symbionts at levels as low as 0.001 percent have shown that most coral colonies harbor multiple strains of *Symbiodinium*. These techniques have shown that coral colonies from four scleractinian species (*Acropora millepora*, *Acropora tenuis*, *Stylophora pistillata*, and *Turbinaria reniformis*) previously thought to harbor only a single *Symbiodinium* clade actually harbor multiple strains (Berkelmans and Van Oppen 2006; Mieog, Van Oppen, Cantin, Stam, and Olsen 2007).

The ability of coral hosts to support several different clades of *Symbiodinium* has led to theories of “symbiont shuffling” (Baker 2003; Goulet and Coffroth 2003; Goulet 2006). Here, the resident *Symbiodinium* algae can compete with each other and create a new combination of the coral and zooxanthellae hologenome from strains that are already within the coral. Low-level background symbionts have the ability to outcompete the dominant clade, given the right environment (Baker 2003). With symbiont shuffling, no new symbionts are introduced from the environment. Rather, the environment places selective pressure on the different types of *Symbiodinium* cells already within the coral tissue. Berkelmans and Van Oppen (2006) have shown that such symbiont shuffling can occur in transplanted populations of *A. millepora* in the Great Barrier Reef. The corals originally have a large population of Type C *Symbiodinium* and minor populations of Type D. Once the faster-reproducing Type C symbionts are expelled from the corals during heat stress, the thermally tolerant Type D zooxanthellae are able to dominate in that particular colony of *A. millepora* transplants.

Moreover, when the surviving *A. millepora* population changes the symbiont from Type C to Type D, their thermal tolerance and photosynthetic yields increase appreciably. It is possible that the thermal tolerance of zooxanthellae is due to the stability of the thylakoid or other lipid membranes of their chloroplasts (Berkelmans and Van Oppen 2006). It is hypothesized that the thermally tolerant D strain of zooxanthellae possesses more stable thylakoid membranes that enable it to cope better with rapid rates of global warming (Tchernov, Gorbunov, De Vargas, Narayan Yadav, Milligan, Häggblom, and Falkowski 2004).

Alternatively, other investigators have proposed that “symbiont switching” could be the major way of changing the dominant population of endosymbionts. Symbiont switching is achieved through the elimination and replacement of the dominant clade of *Symbiodinium* by a new strain of endosymbionts from the surrounding environment. The environment selects which cells survive within the body. While the above-mentioned experiments supported the symbiont shuffling hypothesis, a subsequent study by the same researchers provided evidence for symbiont switching among corals that did not appear to contain a minor, more heat-tolerant, population

of *Symbiodinium* (Jones, Berkelmans, Van Oppen, Mieog, and Sinclair 2008). This may have important ecological consequences, since symbiont shuffling to more heat-resistant types may not be efficient enough to keep up with global climate change, and it may not be possible for many species. Over the next one hundred years, it is predicted that average tropical sea temperatures will increase by 1–3°C (Berkelmans and Van Oppen 2006). Therefore, in order to adapt to the changing environment, coral colonies would greatly benefit from evolving a method of symbiont shuffling or switching.

Pea Aphids and *Buchnera aphidicola*: Taking the Heat

The pea aphid *Acyrthosiphon pisum* and its bacterial symbiont *Buchnera aphidicola* have become a widely accepted model for a mutually obligate symbiosis. That is, neither the aphids nor the bacteria will flourish without their partner. *Buchnera* provides essential amino acids that are absent from the phloem sap diet of the pea aphids (Baumann 2005), and the pea aphids supply nutrients and intracellular niches that permit the *Buchnera* to grow and reproduce (Sabater Muñoz, Van Ham, Martínez Torres, Silva Moreno, Latorre Castillo, and Moya Simarro 2001). Because of this interdependence, aphids are highly constrained to the ecological tolerances of *Buchnera* (Dunbar, Wilson, Ferguson, and Moran 2007). In the field, temperatures ranging from 25° to 30°C result in pea aphids with lower densities of *Buchnera* (Montllor, Maxmen, and Purcell 2002).

A recent study (Dunbar, Wilson, Ferguson, and Moran 2007) showed that heat tolerance of pea aphids and *Buchnera* holobiont could be destroyed with a single nucleotide deletion in the promoter of the *Buchnera ibpA* gene. This microbial gene encodes a small heat shock protein, and the small deletion eliminates the transcriptional response of *ibpA* to heat. *Buchnera* are at least partly able to survive at high temperatures because of constitutive expression of genes that are normally up-regulated in response to heat (Wilcox, Dunbar, Wolfinger, and Moran 2003). It is important to note that secondary symbionts, such as *Serratia symbiotica*, have also been implicated in *A. pisum* response to heat shock (Russell and Moran 2006), suggesting a complex interplay of multiple genomes under thermal stress.

Clones (or “lines”) with this deletion can be maintained in the laboratory, and the deletion is present in field populations, suggesting a selective advantage under certain environmental conditions (Dunbar, Wilson, Ferguson, and Moran 2007). Although pea aphids harboring *Buchnera* with the short *ibpA* promoter allele suffer from decreased thermotolerance, they experience increased reproductive rates under cooler temperatures (15°–20°C). Aphid lines containing the short-promoter *Buchnera* produce more nymphs per day during the first six days of reproduction

compared with aphid lines containing long-allele *Buchnera*. This trade-off between thermotolerance and fecundity allows the pea aphids and *Buchnera* to diversify. Moreover, the holobiont can survive due to changes in the symbiont's genome. As Rosenberg, Koren, Reshef, Efrony, and Zilber-Rosenberg (2007) have pointed out, advantageous mutations will spread more quickly in bacterial genomes than in host genomes because of the rapid reproductive rates of bacteria. In an environment where heat stress is less common, a mutation that increases the reproductive rates of the host (at the cost of heat tolerance) will provide advantages to both organisms. The pea aphids and *Buchnera* both produce more progeny. Depending on the conditions, the survival of the holobiont depends on the type of *Buchnera* inherited. In this manner, variant *Buchnera* genomes can be thought of as alleles for the larger hologenome. Just as certain alleles in a species population may be more advantageous, so certain genomes may be more advantages for the holobiont. Variation in the symbiont genome may be especially important when the host has limited variability, as in the clonal, parthenogenetic populations of aphids.

Conclusions

The examples in this chapter provide evidence that symbiosis and evolution are not separate phenomena. Evolution shapes and selects for symbiosis, while organisms in symbiotic relationships evolve to accommodate one another. Although there is tension between the needs of the individual organisms and the relationships among the symbionts, symbioses continue to exist, implying that symbiosis increases the overall fitness of the individual species involved. The evidence presented here shows that different symbiont subgroups (either clades or mutations) can be selected and affect the fitness of certain populations of holobionts (i.e., what we have traditionally considered as the large individual). I have tried to document several evolutionary ramifications of widespread symbiotic associations.

First, developmental symbiosis appears to be a widespread phenomenon, found throughout arthropods and vertebrates. It is not relegated to remarkable exceptions, such as lichens or squids. Codevelopment may prove to be the rule, not the exception.

Second, symbionts can provide their hosts with signals for development (as when *Wolbachia* provides anti-apoptotic signals for the wasp ovary or *Bacteroides* induces gene expression in the mammalian gut) and for homeostasis (as in the heat tolerance provided by various symbionts).

Third, such symbioses can provide selectable variation. The symbioses of corals with their dinoflagellates and of aphids with their bacteria indicate that genotypic variants of the symbiont can be selected by the environment.

While we have documented that symbionts can provide selectable epigenetic variation for *homeostatic* functions (i.e., thermotolerance), and we have documented cases of developmental symbioses, we have not documented cases wherein allelic or clade differences in the symbiont population effects the *development* of the host in different ways. However, experiments on mice and wasps are pointing in this direction. When mice with mutations in their leptin genes become obese, their guts contain a 50 percent higher proportion of *Firmicutes* bacteria and a 50 percent reduction in *Bacteroides* bacteria than wild-type mouse guts. Moreover, when the gut symbionts from the leptin-deficient mice were transplanted into genetically wild-type germ-free mice, these mice gained 20 percent more weight than those germ-free mice receiving gut microbes from wild-type mice (Ley et al. 2005; Turnbaugh, Ley, Mahowald, Magrini, Mardis, and Gordon 2006). Thus, there appear to be interactions between the genotype of the host and the types of microbial symbionts that are selected by that host environment. Together, a particular symbiont population and a particular host genotype generate a particular phenotype, in this case, obesity. Similarly, Dedeine, Boulétreau, and Vavre (2005) reported that different genotypes of *Asobara* interact differently with *Wolbachia*.

Terrestrial webs of life are predicated on symbioses between plants and their rhizobacterial, endophytic, and mycorrhizal symbionts. As developmental biologists begin appreciating how important symbionts are for animal development, *symbiopoiesis*, rather than *autopoiesis*, appears to predominate. Moreover, the host–symbiont partnership can be a codeveloping, coevolving entity that can be selected by the environment. The symbionts provide an epigenetic source of heritable variation parallel to that of the host genome. They are an acquired inheritance that can produce selectable variation.

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