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1 **Microbial impacts on insect evolutionary diversification: from patterns to**  
2 **mechanisms**

3

4 **Fabrice Vavre & Natacha Kremer**

5

6 **Abstract**

7 Symbiosis can favor rapid shifts in host phenotypic traits, particularly through the  
8 contribution of symbionts to the host's physiology. In addition, variations in the  
9 microbiota composition between individuals can be associated with pre- and post-  
10 zygotic barriers. All together, these phenomena may contribute to insect diversification  
11 and speciation. Recent advances have also shown that the host-microbiota molecular  
12 dialogue, mediated notably by host immune and developmental pathways, is critical for  
13 the acquisition and control of the microbiota, and could also contribute to reproductive  
14 isolation. While still a controversial hypothesis, adaptation through symbiosis could  
15 thus trigger host-symbiont coevolution and accelerate differentiation.

16

17

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21

22

23 **Highlights**

- 24 - Symbiotic communities in insects are shaped by host and environmental cues  
25 - Recruitment and control of symbionts involve host immunity and development  
26 - Symbionts can affect host niche exploitation and modulate pre-mating isolation  
27 - Host-symbiont coevolution can lead to specificity and trigger post-mating  
28 isolation

29

30 **Introduction**

31 Biology is undergoing a paradigm shift. An individual should no longer be considered as  
32 a single organism, but as a chimera composed of a community of interacting organisms,  
33 including the host itself, but also a wealth of microbial partners that are associated with  
34 it. Microbial partners can be extracellular or intracellular, vertically or horizontally  
35 transmitted, beneficial or detrimental, but all contribute to the phenotype of the  
36 symbiotic individual. This phenotype is thus an 'extended phenotype' resulting from the  
37 expression of multiple genomes and their interactions [1].

38 At a macro-evolutionary scale, there is no doubt that symbiosis has played a major role  
39 in the evolution and diversification of entire clades of insects by allowing the  
40 exploitation and/or colonization of new niches [2-6]. For instance, symbionts can  
41 physiologically contribute to the provision of essential nutrients to hosts that feed on  
42 unbalanced food (*e.g.*, plant sap or blood), or to the exploitation of recalcitrant food  
43 sources (*e.g.*, wood) [7,8]. Nonetheless, our understanding of the micro-evolutionary  
44 processes involved in diversification is surprisingly still very limited.

45 The picture is however changing. First, microbiota are described in a growing number of  
46 insect species, which makes now possible the study of the biotic and abiotic factors  
47 shaping their composition. Second, the molecular dialogue between hosts and symbionts  
48 starts to be deciphered, highlighting notably a crucial role of host immune and  
49 developmental pathways in the acquisition of the microbiota and its control. Third,  
50 rapid shifts in microbiota composition have recently been associated with physiological  
51 traits, potentially favoring niche diversification and reproductive isolation. After  
52 reviewing these different aspects, we propose that mechanisms involved in the control  
53 of symbionts (immunity, development) and effects of microbial partners on their host  
54 (niche expansion, reproductive isolation) can reinforce each other and facilitate insect  
55 diversification.

56

57 **Within- and between-species variation in the composition of microbial**  
58 **communities.**

59 With the development of high throughput sequencing technologies, symbiotic  
60 communities - and notably gut microbiota - have recently been characterized in a  
61 number of insect species (review in [8]). While descriptive, these approaches constitute

62 a first hint to elucidate factors involved in the variation of symbiotic communities and  
63 their adaptive value within and between phylogenetically related species.

64 Environment has a clear influence on symbiotic composition. For instance, changes in  
65 diet during life or during development are associated with important variations in the  
66 gut microbiota composition (*e.g.*, *Drosophila* or *Cephalotes* ant microbiota [9,10]), but  
67 other factors, like parasite infection, can also modulate it [11]. Interestingly, a  
68 comparison of 62 insect species from various orders highlighted convergence in the  
69 microbiota composition between distantly related species sharing the same diet [12].  
70 This convergence could partly result from adaptation for optimal exploitation of the  
71 environment. Together with the fact that host-associated communities are highly  
72 different from environmental ones (*e.g.*, [10,13]), and that an important predictor of the  
73 symbiotic composition of individuals is the species they belong to (*e.g.*, [14,15]), these  
74 host-microbiota association patterns suggest a fundamental filtering process during the  
75 stable colonization of the host. This filtering can also occur during symbiont  
76 transmission, as recently shown in beewolf wasps, where inoculation of non-native  
77 protective *Streptomyces* symbionts led to normal colonization, but to an absence of  
78 transmission [16]. Different studies have even evidenced that variations detected in the  
79 composition of the microbiota recapitulate host phylogeny, a phenomenon now referred  
80 as phylosymbiosis [17]. For example, different species of the ant genus *Cephalotes*  
81 display a species-specific microbiota, although individuals from a single species were  
82 collected in highly different environments [18]. Similarly, a phylosymbiotic signal was  
83 found in the wasp genus *Nasonia*, albeit all species were reared on the same  
84 environment [19]. Both species-specificity and phylosymbiosis suggest an influence of  
85 the host-microbiota dialogue on the microbiota composition, with possible co-  
86 divergence in the case of phylosymbiosis.

87 While these studies show that both environmental and host factors influence the  
88 composition of the microbiota, they also underline that host factors are of prime  
89 importance in filtering environmental bacterial communities (figure 1). Evident  
90 directions of research are to determine the contribution of the microbiota to the host  
91 phenotype and the adaptive value of its composition, which remain unknown in most  
92 cases.

93

94 **Immunity and development shape bacterial microbiota.**

95 Within the host, the microbiota resides in specific tissues (*e.g.*, the intestine) that  
96 constitute a specific niche. This host niche is shaped by biotic and abiotic factors (*e.g.*,  
97 temperature, pH, oxygen, metabolites, secreted molecules) that may be under the  
98 control of host and bacterial genes. Recent advances have started to elucidate the  
99 proximate mechanisms involved in the construction of this niche and how these  
100 mechanisms regulate the composition and abundance of bacterial communities.

101 Recent findings on *D. melanogaster* indicate that the immune system plays a central role:  
102 it does not only participate in the regulation of pathogens, but also to the regulation of  
103 resident bacteria and to the homeostasis between resident and pathogenic bacteria  
104 (review in [20]). For instance, the repression of NFκB-dependent antimicrobial peptides  
105 (AMPs) controls the commensal microbial community in the fly gut and limits the  
106 density of the pathogenic *Gluconobacter morbifer* [21]. Indeed, RNAi-silencing of the  
107 negative regulator *Caudal* (IMD pathway), specifically expressed in the posterior midgut,  
108 results in a decrease of commensal *Acetobacteraceae*. This process is followed by the  
109 overgrowth of *G. morbifer*, the induction of apoptosis, and the death of the fly [21].  
110 Interestingly, the microbiota itself can directly modify the niche [22]. For example, uracil  
111 produced by opportunists, but not by resident bacteria, activates the Dual oxidase that  
112 regulates the production of microbicidal Reactive Oxygen Species (ROS) [23,24].

113 In the midgut of the majority of arthropod species, epithelial cells secrete a peritrophic  
114 membrane (PM) which constitutes a critical interface with the microbiota, protecting  
115 the host against pathogenic infections [8,20]. Remarkably, transcription factors and  
116 toxic molecules, by modulating immune pathways (*e.g.*, IMD/relish, JAK-STAT or JNK),  
117 also have a pleiotropic role in host developmental processes [25–28]. Indeed, JAK-STAT  
118 or JNK pathways, which are activated by microbicidal ROS, facilitate the epithelium  
119 renewal [25]. The PM integrity is also directly impacted by gut microbiota in the tick  
120 *Ixodes scapularis*. Indeed, dysbiosed larvae exhibit a reduced expression of STAT that  
121 lowers the expression of the peritrophin, a major glycoprotein structuring the PM [29].  
122 In this case however, the reduced thickness of the PM limits the colonization of the  
123 pathogenic spirochete *Borrelia burgdorferi* [29].

124 A differential regulation of microbial populations can be supported by the development  
125 of anatomical structures where a specific immune regulation is locally triggered. For  
126 instance, the evolution of compartmentalization together with the important anatomical  
127 variation of gut structures and immune regulations between species may be the

128 consequence of the intense selection imposed by symbiosis (reviews in [8,20]). Another  
129 striking example is the confinement of *Sitophilus* primary endosymbiont (SPE) within  
130 the weevil's bacteriocyte (*i.e.*, cells specialized in hosting symbionts) in response to  
131 secretion of AMPs. Indeed, the localized secretion of coleoptericin-A within the  
132 bacteriocytes regulates bacterial growth, initiating the development of giant filamentous  
133 endosymbionts that are not able to spread into insect tissues [30].

134 All these studies highlight the fundamental role of the host-microbiota dialogue in  
135 shaping both immune and developmental homeostasis (Figure 2). This suggests that  
136 coevolution between partners favors the maintenance of specific microbes in a  
137 particular niche, a process which could underlie the establishment of phylosymbiosis  
138 (Figure 1).

139

#### 140 **Symbiont-induced mechanisms favoring diversification and speciation.**

141 While symbionts play an important role in numerous insect functions (review in [31]),  
142 only a few studies directly link the variation of the microbiota - within or between  
143 closely related species - to phenotypic traits potentially involved in diversification and  
144 speciation.

145 The first category of phenotypic traits relates to symbiont-mediated exploitation of the  
146 host ecological niche (review in [32]). The acquisition of symbionts has been associated  
147 with rapid niche shifts in a few cases. For instance, experimental switching of the  
148 *Ishikawaella* symbionts between *Megacopta punctatissima* and *M. cribraria* led to a  
149 complete reversal of the performances of the plataspid stinkbugs on different host  
150 plants, *i.e.* soybean and pea [33]. Another example is the evolution of a variant of the  
151 western corn rootworm *Diabrotica virgifera* in response to the pest control crop  
152 rotation (corn *vs.* non-host soybean). This variant exhibits a shifted microbiota  
153 composition with an increase in *Klebsiella* sp. and *Stenotrophomonas* sp., which could  
154 favor tolerance to anti-herbivory defenses of the new host plant through the increase of  
155 cysteine proteases activity [34]. In these cases, provision of novel traits by symbionts  
156 can support access and/or adaptation to new environments and favor adaptive  
157 radiation.

158 The second category of traits potentially involved in differentiation relates to the impact  
159 of symbionts on the interruption of gene flows between individuals harboring different  
160 microbiota, *i.e.* on host reproductive isolation. Individuals harboring similar

161 extracellular or intracellular microbiota exhibit kin recognition and mate preferentially  
162 together in several *Drosophila* species [35–37]. For instance, the different microbiota  
163 composition of *D. melanogaster* flies fed on different food sources, and particularly the  
164 presence/absence of *Lactobacillus plantarum*, influences the sexual isolation pattern  
165 [35]. In the *D. paulistorum* species complex, infection by *Wolbachia* also influences  
166 mating preference of males and females [37]. These preferences could directly rely on  
167 the modification of pheromonal profiles through the participation of symbionts to the  
168 synthesis of cuticular hydrocarbons or volatile compounds [35], but other mechanisms,  
169 such as a modification in the neuronal integration of the signal, remain to be explored. In  
170 addition, both vertically- and horizontally-transmitted symbionts may participate to  
171 post-mating isolation by inducing hybrid sterility. In the *Drosophila paulistorum* and  
172 *Nasonia* species complexes, sterility is associated with the over-proliferation of  
173 symbionts in the testes of hybrid males [37,38]. While the mechanisms involved are not  
174 known, proliferation of symbionts in hybrids may result from the perturbation of the  
175 genetic interactions between symbionts and host genes involved in the control of the  
176 symbiotic population. Supporting this hypothesis, Brucker et al. (2013) showed that  
177 hybrid viability is restored when gut bacteria are removed from *Nasonia* wasps [17].  
178 Dead hybrids show an altered microbiota, a strong melanization coupled with an  
179 activation of the immune system, suggesting that ‘control’ mechanisms may diverge  
180 rapidly between closely related species, and be involved in post-zygotic barrier to  
181 hybrid formation. This hypothesis has recently been convincingly exposed in [17].  
182 Finally, microbe-microbe interactions can also participate to post-mating isolation. The  
183 most studied example is the hybrid mortality resulting from bidirectional  
184 incompatibility in crosses between individuals infected with different *Wolbachia* strains  
185 [reviewed in 39,40].

186

### 187 **Symbiosis as a driver of insect diversification.**

188 Modifications of symbiotic communities can be extremely rapid both within individuals  
189 and populations. These shifts can reflect selection for symbiont-mediated traits that  
190 allow adaptation to the local environment. For example, *Spiroplasma* has rapidly spread  
191 within *Drosophila neotestacea* populations, owing to the protection it confers against  
192 sterilizing nematodes. These adaptive processes can also be coupled to processes that  
193 are not adaptive for the host. For example, *Rickettsia* rapidly spread in populations of

194 *Bemisia tabaci* in the United States as a result of the benefit it provides on some traits  
195 (e.g., fecundity, developmental time), but also because of the reproductive manipulation  
196 it induces (i.e., female-bias in the progeny) [42]. Whatever the mechanisms involved,  
197 these examples highlight that symbiont frequencies can dramatically change over short  
198 periods of time. Importantly, these rapid changes can dramatically affect the selective  
199 pressures acting on the host to acquire, control and tolerate beneficial and/or prevalent  
200 symbionts [43]. For example, tolerance evolution has been proposed as the fundamental  
201 force that led to the evolution of host dependence in the *Wolbachia* - *Asobara tabida*  
202 symbiosis, as a consequence of the accommodation of the host to the modification of  
203 ROS homeostasis by the symbiont [44–46]. This coevolutionary dynamics of hosts and  
204 symbionts following rapid changes in microbiota composition could have dramatic  
205 consequences on hybrid viability, as shown in *Nasonia*.

206 All together, symbiosis could thus trigger insect differentiation through a variety of  
207 mechanisms. Symbionts, by providing new physiological capabilities to their hosts, can  
208 allow niche expansion, a first step towards adaptive radiation. In addition, acquisition  
209 and spread of a new symbiont may be accompanied by side effects that facilitate or  
210 trigger host differentiation. First, facilitation can occur when individuals harboring the  
211 same microbiota exhibit mate preference. Second, host genes underlying local  
212 adaptation may not only encode traits directly involved in niche exploitation, but also  
213 genes involved in the adaptation to the symbiotic partner, such as immune and  
214 developmental genes. Rapid evolution of these genes may favor the emergence of post-  
215 zygotic barriers and increase host-symbiont specificity, thus allowing niche segregation  
216 and rapid differentiation.

217

## 218 **Conclusion**

219 For a long time, global phylogenetic patterns have suggested that symbiosis is an  
220 important driver of insect diversification. Recent advances in symbiont-mediated  
221 behavioral modifications and in the mechanisms involved in symbiotic homeostasis now  
222 highlight proximate mechanisms through which this could occur. Studies of symbiosis  
223 diversification at a short time-scale are needed to get a better picture of the selective  
224 pressures and processes involved in the evolution of symbiotic relationships, and of  
225 their role in the diversification of insects. A full understanding of these processes  
226 requires to expand our documentation on the variations of community composition, but



227 more importantly on the mechanisms underlying host-symbiont interactions within  
228 species, between biotypes/host races or closely related species. New methodologies are  
229 offering a unique opportunity to tackle these questions, providing a full description of  
230 the composition and the functioning of these interactions and facilitating the detection  
231 of host genes involved in local adaptation. Are those genes frequently associated with  
232 the regulation of the symbiotic compartment? How do they influence hybrid  
233 performance and viability? Studying the mechanisms of host-symbiont interactions and  
234 their micro-evolutionary dynamics is thus a crucial step for the field of insect symbiosis  
235 in particular, but more importantly for the entire field of entomology.

236

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238

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243 **Figure legend:**

244

245 **Figure 1: Processes of variation in microbiota composition.** When symbionts are  
246 environmentally acquired, bacterial composition within the host depends on the  
247 microbial composition of environmental communities. A plastic composition of the  
248 microbiota may be adaptive when the environment fluctuates rapidly and without  
249 predictability. This could for example be the case in *Drosophila melanogaster*, where the  
250 local environment, among which diet, has an extreme influence on the composition of  
251 the microbiota [9,47]. Numerous examples also indicate an active filtering process,  
252 which results in the selection of a subset of the environmental community and an  
253 increase in the host/microbiota specificity. The phylosymbiotic signal observed in some  
254 instances may reflect (co)evolution of the host-symbiont interactions. Circles of different  
255 colors represent bacterial strains/species and rectangles host genotypes.

256

257 **Figure 2: Host-microbiota dialogue shapes both immune and developmental**  
258 **homeostasis to control the microbiota composition.** Molecular pathways (*italics*)  
259 exhibiting a pleiotropic role in immunity and development must play a particularly  
260 important role in defining and maintaining the specificity of the interaction in a  
261 particular host niche.

262

263 **Figure 3: Model for the role of symbiosis in the reinforcement of differentiation**  
264 **between populations.** Symbionts can promote rapid adaptation to local conditions.  
265 Rapid shifts in microbiota can also generate selective pressures on the partners for  
266 optimization of symbiont acquisition and/or for tolerance. As a consequence, host-  
267 microbiota specificity should increase, leading to a reduction in hybrid performance.  
268 Furthermore, host-symbiont coevolution can lead to symbiont-mediated  
269 incompatibilities between hosts adapted to different microbiota, reinforcing specificity  
270 and thus niche segregation between hosts harboring different microbiota. This scenario  
271 can be applied when microbiota diversification occurs in allopatric populations. In the  
272 case of sympatric/parapatric populations, reinforcement mechanisms possibly  
273 mediated by symbionts, such as niche fidelity or mate choice would be required.

274

275

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Figure 1:

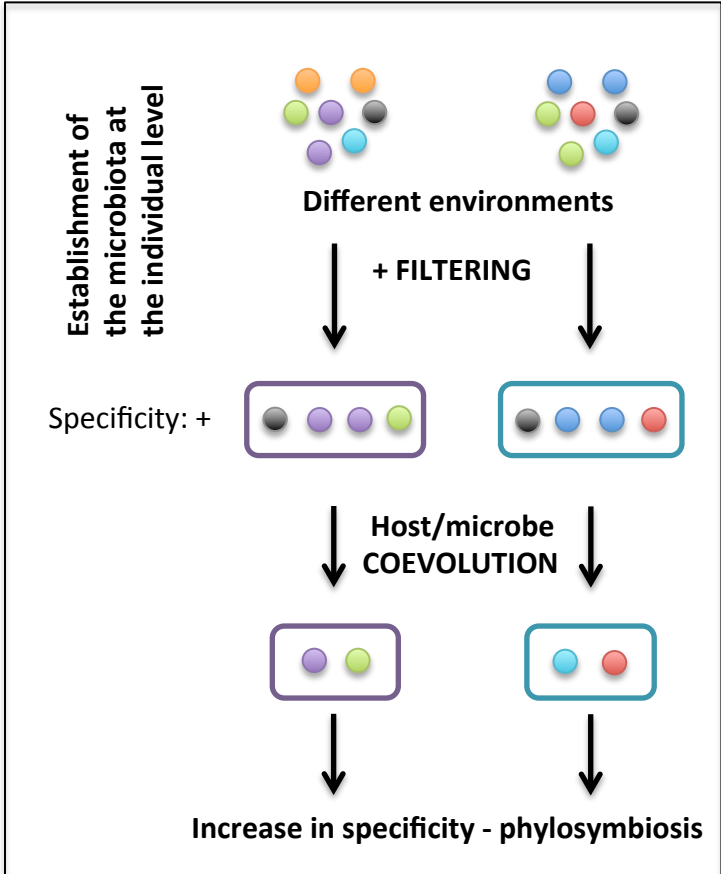




Figure 2:

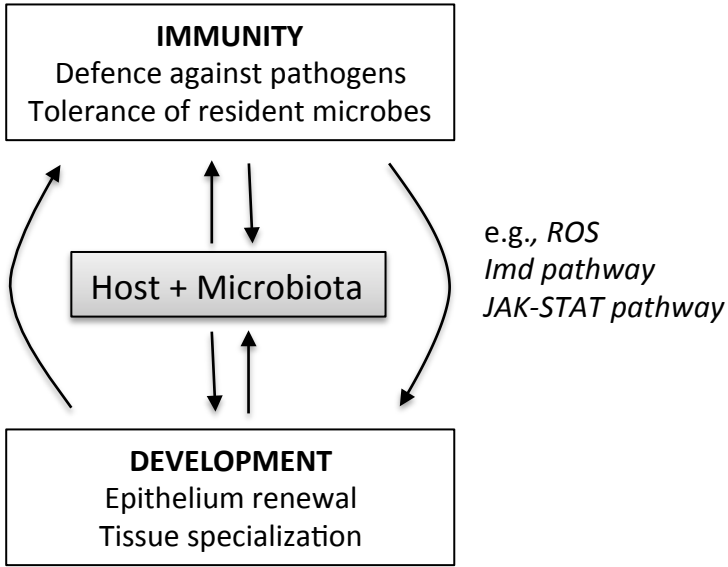


Figure 3:

