Symbiont-mediated functions in insect hosts

Qi Su,[1] Xiaomao Zhou[1],* and Youjun Zhang[2],*

[1]Institute of Pesticide Science; Hunan Agricultural University; Changsha, PR China; [2]Department of Plant Protection; Institute of Vegetables and Flowers; Chinese Academy of Agricultural Sciences; Beijing, P.R. China

The bacterial endosymbionts occur in a diverse array of insect species and are usually rely within the vertical transmission from mothers to offspring. In addition to primary symbionts, plant sap-sucking insects may also harbor several diverse secondary symbionts. Bacterial symbionts play a prominent role in insect nutritional ecology by aiding in digestion of food or supplementing nutrients that insect hosts can't obtain sufficient amounts from a restricted diet of plant phloem. Currently, several other ecologically relevant traits mediated by endosymbionts are being investigated, including defense toward pathogens and parasites, adaption to environment, influences on insect-plant interactions, and impact of population dynamics. Here, we review recent theoretical predictions and experimental observations of these traits mediated by endosymbionts and suggest that clarifying the roles of symbiotic microbes may be important to offer insights for ameliorating pest invasiveness or impact.

Introduction

As multicellular organisms, insects as a group seem to be most tolerant of foreign organisms and live together with many different microorganisms, both inside and outside their bodies, in a variety of ways,[1] and symbiotic relationships range from mutually beneficial (mutualism) to neutral (commensalism) or parasitic (parasitism). The microorganisms inside insects include gut microbe, endoparasities, extracellular symbiosis, and intracellular symbiosis (also called endosymbionts). The endosymbionts is the most intimate association between two different organisms, and it is generally reasoned that the association is maintained through the host's generations because the host and symbiont equally benefit from the association.

The endosymbiotic bacteria of insects are prevalent and categorized into two groups: primary symbionts (P-symbionts) and secondary symbionts (S-symbionts).[1] The P-symbionts are obligatory and mutualistic to the host as they play prominent role in insect nutritional ecology by providing essential nutrients that are limited or lacking in the diet or aid in digestion and detoxification of food,[1-3] such as *Buchnera aphidicola* in aphids,

Portiera aleyrodidarum in whiteflies, *Carsonella ruddii* in psyllids, and *Tremblaya princeps* in mealybugs.[1] The P-symbionts typically housed in specialized host organs termed bacteriocytes and relayed within transovarial transmission from mothers to offspring with perfect fidelity.[1,4,5] In contrast to primary symbionts, S-symbionts may not be required for host survival and the association between host and symbiont is generally not very intimate and inhabit a variety tissues including primary bacteriocytes,[6,7] secondary bacteriocytes and sheath cells,[8,9] salivary glands,[10,11] Malpighian tubules (Bution et al., 2008),[12] and reproductive organs.[11,13,14] The roles of more and more S-symbionts to their hosts have been unveiled in recent years, and these symbionts may exert diverse effects on their host, such as defense against natural enemies by enhancing host resistance,[2,15,16] mediate thermal tolerance of their hosts,[17] to facilitate use of novel hosts[18] and so on. Most of these S-secondary symbionts with the primary symbiont inside the bacteriocytes, however, some S-symbionts localize outside the bacteriocytes and suffer occasional horizontal transmission, occur at low titers in hosts within and between species.[10,13,19,20]

The remarkable bacterial associations in insects were deemed intractable to study. In particular, all attempts to isolate the symbionts into axenic culture failed; consequently, the bacteria identification and the relationship could not be easily manipulated. Our understanding of the connection between symbiotic bacteria and insects under natural contexts in a population ecology condition has two different approaches over the last decade, largely through treated with antibiotics to eradicate the bacteria from insects or providing food lacking nutritional substances putatively provided by the endosymbionts[21-24] and deduced from their complete genome sequence and subsequent gene expression studies.[25-27]

In this review, a wide range overview of the diverse roles of endosymbionts on insect host ecology and future aspects such as the potential role of endosymbionts in pesticide detoxification and effect of endosymbionts on host behavioral ecology has been discussed. Symbiosis function and insect traits are influenced by the total complement of insect-symbionts interrelationships. A firm understanding of these interactions will lead to a better appreciation of these astonishing symbioses and may provide insights for novel approaches to pest management.

Defense Toward Pathogens and Parasites

Most insects suffer attacks from various natural enemies, including pathogens, parasites, predators, and parasitoid wasps.

Variation in resistance toward parasites and pathogens has been shown to be regulated by the secondary symbionts in a number of insects and an understanding of such mechanism is steadily increasing. In support of the theoretical predictions, several natural examples of symbiont-mediated protection have been reported recently in insects, and these are discussed below.

To data, one obligate endosymbiont, *Buchnera* and several different facultative endosymbionts, namely *Hamiltonella defensa*, *Regiella insecticola*, and *Serratia symbiotica* as well as *Rickettsia*, *Rickettsiella*, *Spiroplasma*, and *Arsenophonus* have been reported from aphid species.[2,28] The variable susceptibility of pea aphids to *Aphidius ervi* predation is linked to the presence or absence of the aphid's facultative endosymbionts. Oliver et al. (2003) showed that both *H. defensa* and *S. symbiotica* could increase aphid host resistance against *A. ervi*, a parasitoid wasp that commonly preys on aphids. These symbionts do not prevent *A. ervi* oviposition in the aphid but developmental success of wasps following parasitism were reduced by causing high mortality in developing parasitoid larvae in aphid hosts.[15,29] *R. insecticola*, another common bacterium, provides strong protection against parasitic wasps, suggesting that the ability to protect their host against natural enemies may evolve readily in multiple species of endosymbiotic bacteria.[30] Recent studies strongly suggested that several phage-borne toxin genes and several toxins, which provided defense to the aphid host, identified depended on the genome of the *H. defensa*.[8,31,32] The potential for phage to encode additional toxin genes provides a mechanism by which normally genetically stable and isolated bacterial endosymbionts could rapidly acquire novel toxins. This increases the endosymbionts' potential to protect their insect host and provides an opportunity for additional protective genes to be introduced into these symbionts. Phage ecology is an underexplored facet of symbiosis, in relation to what is known about bacterial symbionts, and future investigations into phage and the way that they deliver their toxins to the parasitoid wasp without harming the aphid host will solve many remaining questions about this system. Consequently, it is thought that the phage-borne toxin genes that target and kill the parasitoid wasps. Further experimentation, however, is required to confirm that these putative toxins are the active compounds that facilitate *H. defensa* protection. Similarly, the molecular basis of *H. defensa*-mediated resistance is yet to be resolved.

The bacterial symbiont *R. insecticola* protects pea aphids from the entomophthorales fungus Pandora (Erynia) neoaphidis,[33] and recently, Lukasik et al. (2012)[34] reports that four distantly related symbionts (in the genera *Regiella, Rickettsia, Rickettsiella* and *Spiroplasma*), can reduce mortality and also decrease fungal sporulation on dead aphids which may help protect nearby genetically identical insects. Thus, *R. insecticola* not only protects individual insects but also protects the host population. The mechanisms involved in *R. insecticola*-mediated protection have not yet been determined but could involve the synthesis of antifungal molecules, as has been observed in other insect-symbiont systems.[35]

Wolbachia are maternally inherited bacterial endosymbionts that infect at least 20% of all insect species, making them extremely common in nature.[36] In many insect hosts, *Wolbachia* is usually considered to mediate reproduction of the hosts either enhance the proportion of infected female hosts or kill male offspring.[36,37] *Wolbachia* are found in a variety of tissues and cell types within the model insect *Drosophila melanogaster*, providing an opportunity for it to interact with infectious intracellular pathogens.[13] If *Wolbachia* provides protection from infectious pathogens, this would provide the host with a fitness advantage and serve as a mechanism to drive *Wolbachia* invasion in *D. melanogaster* populations. Recently, *Wolbachia* has been manifested to confer enhanced resistance toward various insect RNA viruses in dipterans,[38,39] such as *Culex quinquefasciatus* or *Aedes aegypti*.[40,41] The enhanced resistance mediated by *Wolbachia* might be regulated by resistance to virus accumulation, tolerance of virus infection or a combination of both mechanisms and from the host's innate immune system being primed by both *Wolbachia* and a virus.[40]

Symbiont-mediated protection could provide *Wolbachia* with an additional mechanism by which to invade insect populations. Natural Australian populations of *D. melanogaster* maintain a stable strain of *Wolbachia* infection; the tropical and subtropical northern populations are heavily infected (greater than 95%), but the cooler temperate southern populations are poorly infected (~15%).[42] How this cline is maintained is unclear, but it is independent of local climatic conditions.[43,44] It is tempting to speculate that virus infection rates could be higher in northern populations and, hence, promote the persistence of *Wolbachia* in these populations.

Symbiont-mediated protection against fungal pathogens has also been observed in the attine ants[45] and a beetle that feeds on pine trees.[46] Attine ants have long been a fascination for symbiosis researchers because of their unique ability to "farm" Lepiotaceae fungi as a food source. The delicate balance between ant and fungi can be disrupted when other fungi, which are not used as a food source. Remarkably, a *Streptomyces* sp bacterial symbiont found on the exterior of ants produces an antifungal agent that kills non-Lepiotaceae fungi.[45] By killing off these invading fungi, the *Streptomyces* symbiont protects the fungal symbiont and, in turn, ensures the long-term survival of its ant host. A different *Streptomyces* symbiont isolated from the Southern pine beetle, *Dendroctonus frontalis*, was also observed to protect an important fungal symbiont from competing fungi. An antifungal molecule derived from the Streptomyces symbiont was identified and shown to only interfere with the antagonistic fungi.[46] There is also evidence that wasp larvae might be protected from microbial-induced mortality by a related *Streptomyces* symbiont.[47]

Influence on Insect-Plant Interaction

Insects have evolved many strategies to feed on plants including associations with mutualistic symbionts, which can be important mediators of direct and indirect interactions between herbivorous insects and their host plants.[48] The most striking ecological character conferred to insects by endosymbionts is their role in supplying essential nutrients to their hosts. As several reviews have speculated that the role of primary endosymbionts in insect

nutritional ecology,[1,49,50] recent research in the role of secondary endosymbionts in mediating plant-insect interactions will be discussed.

Several recent studies suggested that food plant use of herbivorous insects can be directly enhanced by facultative endosymbionts. One paper recently published by Tsuchida et al. (2011) showed injection of a secondary symbiont *R. insecticola* from a clover-adapted pea aphid to vetch aphid *Megoura crassicauda* allowed the latter that normally could not feed on clover to use this host plant. Transfection experiments in pea aphids indicated that *R. insecticola* enhances reproduction on clover.[51,52] However, antibiotic manipulation was used to experimentally remove *R. insecticola* from naturally infected lineages showed that *R. insecticola* was not responsible for generating the tradeoff on vetch and clover (Leonardo, 2004).[21] Moreover, artificial infection with *R. insecticola* reduced acceptance of aphids for both two plants.[52] Thus, although *R. insecticola* affect host performance as well as host acceptance behavior in aphids, the impact of the symbiont is not necessarily positive and seems to be context dependent.

The stinkbugs, wherein the host-symbiont associations can be easily manipulated, provide a novel system that enables experimental approaches to previously untouched aspects of the insect-microbe mutualism.[53] As in aphids, the endosymbionts of *Megacopta* stinkbugs are correlated with food plant use. A pest stinkbug species, *Megacopta punctatissima*, performed well on crop legumes, while a closely related non-pest species, *Megacopta cribraria*, suffered low egg hatch rate on the plants. When their obligate gut symbiotic bacteria were experimentally exchanged between the species, their performance on the crop legumes was, strikingly, completely reversed: the pest species suffered low egg hatch rate, whereas the non-pest species restored normal egg hatch rate and showed good performance.[54] It is not clear though how the symbiont facilitates usage of the crop legumes. The symbiont of the pest species *M. punctatissima* may either perform better on the crop plants, e.g., by aiding in detoxification of a plant secondary compound, or may provide nutrients lacking on potentially suboptimal crop plants.[54] Endosymbionts can also be important mediators of indirect interactions that limit use of food plants. For instance, the hosts that provide defect amino acids in the phloem have improved levels of secondary symbionts of aphids. However, as the secondary symbionts do not devote to amino acid nutrition for the aphids, negative effects of low quality phloem on aphid performance are aggravated.[55,56]

Insect symbionts have been reported to benefit their hosts, which took the form of physiological changes in the plant, mediated by a complex signal-transduction response to insect attack.[57-59] Perhaps the best known example is ambrosia beetles and their mutualistic fungi of bark, which make wood digestible for their hosts' larvae and assist the beetles in overcoming tree resistance mechanisms.[60] A microarray experiment revealed that the regulation of defense-related genes in the plant was influenced by the symbiont *Wolbachia* in corn root borer.[61] Similarly, the expression of plant defensive pathways in tomato was associated with the high concentrations of the symbiont *Candidatus* Liberibacter psyllaurous in tomato psyllid, bactericerca cockerelli.[62] Insect herbivores have been reported to manipulate directly host plant physiology for their own benefit.[58] For example, the potential to modulate plant defense in chewing insects are the symbiotic gut flora found in saliva and regurgitant, which is to synthesize N-acylamino acids.[63,64] Another possible example is found in the apple leaf-mining moth, whose endosymbiont *Wolbachia* is involved in the production of cytokinins, which inhibit senescence, maintain chlorophyll, and control nutrient mobilization.[65,66] The presence of *Wolbachia* in the larvae of the leaf-miner is positively correlated with high levels of cytokinins, which induced the "green-island" formation on leaves, increased compensatory larval feeding and higher insect mortality.[66] Currently the mechanism of how *Wolbachia* manipulates plant physiology during the plant-herbivore interaction is not known.

Insect symbionts may benefit their hosts by facilitating the transmission of plant pathogens. As we all known, almost 80% of the virus inflicted to plants is due to insect vector transmission.[67] Virus particles can cause circular infections in the aphids and whiteflies by binding to the GroEL chaperone proteins produced by symbiotic bacteria,[68,69] which seems to protect begomoviruses in insect hemolymph and thereby affects the ability of insects to transmit virus.

Adaptation to Environment

So far, there is more and more attention to the abiotic factors to the effect of endosymbionts on temperature tolerance of their insect hosts. The range and variability of temperatures that an organism can tolerate is an important factor in determining its geographic range. Although the aphid host itself may not be adapted to higher temperatures,[2] again the number of bacteriocytes of the primary endosymbionts *Buchnera* that supplies essential nutrients to the host, has been shown to decrease dramatically at higher temperatures or heat shock (Montllor et al., 2002),[70] however, the secondary endosymbiont *S. symbiotica* and *H. defensa*, which can confer tolerance and a trend toward higher fitness when subjected to high temperatures,[70-72] presumably by enhancing retention of secondary bacteriocytes, as negative effects on the primary bacteriocytes under heat stress. A plausible explanation is suggested by recent findings that *S. symbiotica* can partially rescure *A. pisum* fitness in the absence of the obligatory *Buchnera*.[22] Thus, the heat tolerance of aphid hosts could originate from complementation of *Buchnera* function. Another explanation is the bacterial chaperone groEL, which is constitutively overexpressed in primary and secondary endosymbionts,[73,74] may also protect host proteins from heat degradation when circulating in the hemolymph. An additional evidence for improved heat tolerance has been previously documented for *A. pisum* infected with *S. symbiotica*, which increased host fecundity under constant rearing at 25°C.[75] For whitefly *Bemisia tabaci*, the secondary endosymbiont *Rickettsia* may confer heat tolerance to the host. In this example, *Rickettsia* in *B. tabaci* under normal conditions induces the expression of genes required for temperature tolerance that under high temperatures, indirectly lead to this tolerance.[76] Variation in the genome of *Buchnera* itself adds to variation in heat tolerance of the pea aphid. A single-base regulatory mutation of a heat-shock gene in *Buchnera* of aphids that

eliminates expression of the heat-shock gene under thermal stress and lowers the ability of hosts to endure heat stress and produce hardly any offspring after a short exposure to heat stress.[17]

Besides the direct effects on the insect hosts, temperature cause indirect effects via changing the amounts of symbionts within the host or their efficiency of transmission to the offspring. For example, *Wolbachia*-induced effects of cytoplasmic incompatibility and parthenogenesis are weakened by exposing insects to heat, presumably due to the negative effect of high temperatures on symbiont survival.[77] In *A. pisum*, the survival of *Buchnera* symbionts reduced stemmed from a heat shock treatment.[78] Similarly, high temperature or heat stress dramatically reduced the number of bacteriocytes (in which the obligate symbiont, *Buchnera*, resides) in aphids; however, the presence of *S. symbiotica* gave birth to retain their bacteriocyte.[70]

Body color is an important ecologically trait of visual cues for the pea aphid affects their susceptibility to parasites and predators. The aphid exhibits a color polymorphism, which improve their ability of resistance to natural enemies. Ecological studies showed that red aphids were more likely to be preyed on by predators ladybird beetles on green plants,[79] while green aphids suffer higher rates of parasitoid wasps attack.[80] The pea aphid carried the secondary endosymbiont *Rickettsiella* infection increased the amounts of blue-green polycyclic quinines changes the body color of host from red to green.[28] Thus, the effect of the endosymbiont on body color is expected to influence prey-predator interactions.

Impact of Population Dynamics

Endosymbionts can sharply influence population dynamics via various ways, such as cytoplasmic incompatibility (CI), parthenogenesis induction (PI), feminization, and male-killing. The endosymbiotic bacteria such as *Wolbachia*, *Arsenophonus*, *Spiroplasma*, and *Cardinium* manipulated host reproduction are widespread among arthropods by vertical transmission.[81,82] Cytoplasmic incompatibility, in which uninfected female mated with infected males result in sterile crosses produce few or no offspring,[82] and can be either unidirectional or bidirectional, thus gene flow between these strains is decreased due to a reduction in efficient migration rates. Feminization and Male-killing distort sex-ratio within a population and reduce the uninfected part of population size in which few male will be left to mate a large number of females.[83] Parthenogenesis induction, in which haploid host eggs are converted into viable diploid female offspring, may result in rapidly decline of genetic diversity.[83]

Among these symbionts, *Wolbachia* dominate current research in part because of the widespread and importance of this symbiont. *Wolbachia* can induce cytoplasmic incompatibility in the butterfly, *Eurema hecabe* and parasitoid wasp, *Encarsia pergandiella*.[84,85] Recently, other novel lineage of bacteria has been shown to be related to several reproductive manipulations, including "*Candidatus* Cardinium hertigii" in parthenogenesis induction in parasitoid wasps, *Encarsia hispida*[86] and feminization in the mite, *Brevipalpus phoenicis*,[87] *Rickettsia* related with parthenogenesis induction in leafminer, *Liriomyza trifolii* in Japan[88] and male

killing in the ladybird beetle, *Adalia bipunctata*,[89] or the bacteria *Spiroplasma* and *H. defensa* induces male killing in ladybird, *Cheilomenes sexmaculata*.[90,91] The spread of these bacteriums can result in rapidly decline of population genetic diversity and drive small populations to extinction.[83]

As a few hosts harboring facultative endosymbionts have shown negative effects under some circumstances,[71] while most studies have indicated that secondary symbionts provided fitness benefit, and these symbionts can spread rapidly within host population.[92,93] The endosymbionts relevant to dispersal may also influence population dynamics of insect hosts. Pea aphids containing *R. insecticola* produced only fewer numbers of winged offspring in response to crowding than those lacking this endosymbionts, and for two out of three aphid lineages, the timing of sexual reproduction in response to crowding conditions was changed by the presence of this symbiont.[94]

Pesticide Detoxification

Chemical insecticides are widely used for controlling agricultural pest insects and other organisms worldwide. Meanwhile insecticide abuse has often gave rise to the development of insecticide resistance in various pest insects, whose mechanisms have referred to evolutionary changes in pest genomes such as alteration of pesticide target locus, upregulation of degrading esterases, and improvement of pesticide secretion.[95] Here, we report a mechanism of insecticide resistance previously unknown via an insecticide-degrading bacterial symbiont establishes in pest insects. Kikuchi et al. (2012)[96] reported an extension of this repertoire of effects-bacteria in the genus *Burkholderia* imparts protection against organophosphorous pesticides in stinkbugs. Previous study suggested that biological insecticides, such as *Bacillus thuringiensis*, depended on the interaction with symbiotic bacteria can be involved in insect resistance.[97] Given the general detoxification ability of microbes and their ability to evolve quickly, they could provide a potent means for rapid acquisition of pesticide resistance in hosts. As lateral gene transfers (LGTs) between symbionts and hosts are now known to be common.[98] Therefore, it would not be surprising that this transmission manner would more readily link beneficial pesticide-degrading bacteria to their hosts, enhancing increase of both partners and therefore spread of the resistance phenotype.

Behavioral Manipulation

In mutualistic associations, the evolutionary interest of the symbiont modifies host behavior, which is adaptive to the parasites or predators and such phenomena called "manipulation by parasite."[99,100] However, symbiont-mediated alteration of the host behavior that enhances their probability of transmission has been, to our knowledge, scarcely attention. However, alterations in behavior characteristic by such mutualistic endosymbionts may be common as the examples on superparasitism behavior and reproductive behavior of parasitoid wasp,[101,102] dispersal behavior of money spider[103] or enhanced wandering behavior of stinkbug nymphs.[104] Thus, symbiont-induced alteration of host behavior might be well-known among mutualistic associations than

previously envisioned, particularly with symbiont transmission demands behavioral elements. As the symbionts and the hosts both benefit from the behavior, the behavior might have been evolutionarily favored by host immune system acting on both the partners, whose influence may produce important insights into host physiology.

Conclusions

The increasing awareness of the significant functions that endosymbionts play in host has brought to a rapid increase in the identification of important characteristic attributed to endosymbionts. The revolution in our understanding of the roles of symbionts has been made possible by the many advances in molecular biology and functional genome research. Due to these advanced techniques it is now becoming viable to unravelling the mechanistic basis of the molecular and biochemical mechanisms that underpinning insect-symbionts interaction, and host ecology influenced by these symbionts. Understanding these factors may give us insights into ecological significances of endosymbiont infection, the short and long-term evolutionary tracks they mediate, the ecological differentiation and adaptation to host, the responses to environmental alteration, and species extinction risk.[105] The potential invasion of new pests has often been facilitated by their mutualists and some novel interactions have resulted in new and more virulent insect pests.[106,107] Manipulating symbionts may be exploited to improve pest control and finding out more about insects and their microbial associates will be both fascinating and useful.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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