Abstract

The host-symbiont relationship is complex and, in the case of pathogenic symbionts, can be devastating to host health. Attempts to analyze the variability in host-symbiont interactions have included the effects of abiotic factors such as salinity and temperature, but the influence of other symbionts of the same host is not often considered. There are several examples that demonstrate that the symbionts also associated with the host can modify the host-pathogen dynamic. The bacterial endosymbiont *Wolbachia* confers resistance to viruses and malaria-causing protist parasites in their insect hosts. Wild bumblebees, whose populations have been negatively impacted by pathogens, have intestinal microbes that decrease trypanosome infection level. Intestinal bacterial symbionts can also increase the host's susceptibility to infection, as is the case with intestinal virus infection and possibly some bacterial infections. These examples demonstrate that the interactions of all symbionts associated with the host need to be considered when studying the role of pathogens in host health.

Introduction

Symbioses between microbes and their hosts are prevalent and capable of strongly influencing the host's health, both beneficially and harmfully. The host-symbiont relationship is complex and, in the case of pathogenic symbionts, can be devastating to host health. Due to the varied effects of microbial symbionts on their host, there has been an effort to classify their interactions. In the early days of microbiology, many were seen as the causative agents of disease. Still, some were recognized as beneficial; Louis Pasteur, who was the first to identify pathogenic bacteria, connected the important act of fermentation with the proliferation of microbes. Today, symbiont designations fall along a continuum, from parasitic to mutualistic. Parasitic symbionts, such as *Plasmodium*, the microbe responsible for malaria infection in humans, benefit from the host-microbe relationship at the host’s expense. Alternatively, the host and microbe both benefit in a mutualism. Symbiont microbes vary widely in their functions. Some provide vital nutrients, while others aid with the digestion of food, synthesize vitamins, and inhibit the growth of pathogens in their hosts’ intestine (Kamada et al., 2012). Many microbes can confer important benefits for the host, including increased resistance to stress factors like heat and production of crucial proteins for host functions other than digestion. Some symbionts are considered “reproductive manipulators” and can alter the evolutionary trajectory of their host by creating barriers to gene flow (Moran, McCutcheon, & Nakabachi, 2008). These symbionts interfere with host reproduction so that the symbiont might increase in frequency. A recent study found that intestinal bacteria can alter personality traits in mice (Neufeld, Kang, Bienenstock, & Foster, 2011).
Due to the complexity of many symbiotic relationships, host-microbe relationship models need to consider the environment in which a symbiont and its host are interacting. Abiotic factors, such as salinity, can affect the composition of bacterial cells (Lozupone & Knight, 2007). These environmental factors can also change the relationship between a symbiont and its host. Dinoflagellate endosymbionts of the genus *Symbiodinium* provide almost all nutritional substances to their coral hosts, but, with the recent rise in sea temperatures, many corals have lost their *Symbiodinium* symbiont. This would normally result in near certain death for the coral, but some *Symbiodinium* has been found to survive despite the temperature increase (Berkelmans & van Oppen, 2006). This means that *Symbiodinium* not only contributes nutritional compounds to the host, but also confers a sort of heat resistance, thereby changing the parameters of their symbiosis.

While efforts to analyze the variability in host-symbiont interactions have typically included the effects of abiotic factors such as salinity and temperature, the influence of other symbionts of the same host is rarely considered, although symbiont communities, which form the environment in which pathogens function, are capable of similarly influencing the host-pathogen dynamic. Kopp lab has recently compared yeast and bacterial symbionts in the same host (Chandler, Eisen, & Kopp, 2012). Though no correlation was seen, characterizing all symbionts which co-inhabit the same host is necessary for an accurate model of symbiont pathogenicity. I will provide three examples where other symbionts were found affecting the host’s resistance to pathogen colonization and infection.

The first example of this type of relationship is *Wolbachia*, a bacterial endosymbiont of many arthropods and a few nematodes. Though its influence on host reproduction is well known, it was recently found that *Wolbachia* affects insect immunity to viruses (Teixeira, Ferreira, & Ashburner, 2008) and parasites such as *Plasmodium* (Moreira et al., 2009). The next example deals with agriculturally valuable bumble bee populations that have been in decline due in part to the spread of pathogens. A recent study suggests that the microbiota found in the gut of these social insects offer resistance to a major parasite, *Crithidia bombi* (Koch & Schmid-Hempel, 2011). Finally, we consider evidence for the positive effect of the intestinal microbiome on the pathogenicity of parasites. In this case mice were used as a mammalian model to study the effects of intestinal microbes, as a whole, on virus virulence (Kuss et al., 2011).

**Wolbachia aids in insect pathogen resistance**

*Wolbachia* is a widespread bacterial endosymbiont whose function, until recently, was thought to be solely as a reproductive manipulator. *Wolbachia* can control mating success via a mechanism known as cytoplasmic incompatibility, which causes the death of the offspring of uninfected and infected individuals (Turelli & Hoffmann, 1995). Often female hosts will experience increased fecundity as a result of the infection.

*Wolbachia* is a prevalent endosymbiont, and can infect up to 80% of a population of the fruit fly *Drosophila melanogaster* in the wild (Verspoor & Haddrill, 2011). It has been estimated that 30% of laboratory stocks of *D. melanogaster* are infected with *Wolbachia* as well (Clark, Anderson, Cande, & Karr, 2005). Given the pervasiveness of the endosymbiont in natural and laboratory settings, fully understanding their role in the host should be a priority since unknown roles could skew experimental results. A prime example of this
is seen in the accidental discovery of \textit{Wolbachia}’s effect on host pathogen resistance.

Interested in \textit{D. melanogaster} pathogen resistance, Teixeira, Ferreira, and Ashburner screened for virus sensitive mutants, looking for new genes that aided in resistance to \textit{Drosophila} C Virus (2008). Strangely, their controls were more sensitive to the virus than their mutants, which they realized was due to the control’s antibiotic treatment. A maternally inherited intracellular bacterium was recognized as the source of the viral resistance, and, after sequencing bacterial DNA from resistant embryos, that bacterium was identified as \textit{Wolbachia}.

This example is central in the support for full characterization of known symbionts. Not only does this suggest that prior experiments may be incomplete in their analysis of \textit{Drosophila}’s pathogenic defenses, but also, in light of the fact that \textit{Wolbachia} is found in a wide variety of arthropods such as mosquitoes, this information may prove useful for future studies in medically important areas, such as malaria control.

\textit{Plasmodium}, the parasitic protist responsible for malaria infections, and the \textit{Anopheles} mosquito, the vector for \textit{Plasmodium}, have been at the center of disease control research aimed at reducing infection rates in humans. Recent understanding of \textit{Wolbachia}’s role in host pathogen resistance has given rise to the idea that it can be used as a biocontrol tool. Introduction of strains of \textit{Wolbachia} normally found in \textit{D. melanogaster} could result in the reduction of the \textit{Plasmodium} parasite, given that lab tests with \textit{Wolbachia} decrease \textit{Plasmodium} infections by 75-84\% (Kambris et al., 2010). This may be the result of both \textit{Wolbachia} and \textit{Plasmodium} competing for the same host resource, such as cholesterol (Walker & Moreira, 2011).

\textit{Wolbachia} can be used in other insects which act as vectors for human diseases, such as the \textit{Aedes} mosquitoes that spread dengue fever. There has been successful \textit{Wolbachia} introduction into wild populations of mosquitoes, resulting in an increase in \textit{Wolbachia} frequency 90\% in just 5 weeks (Hoffmann et al., 2011). Additionally, \textit{Wolbachia} can reduce the infection of the mosquitoes by a variety of pathogens, not just those responsible for dengue fever (Moreira et al., 2009).

\textbf{Bumble Bee’s intestinal microbiome confer resistance to devastating pathogens}

Bumble bee population has been in decline since the 1950s, as many natural populations are pushed out of their normal habitat by agricultural intensification and land development (Dupont, Damgaard, & Simonsen, 2011). Population decline of commercial and wild populations will likely have devastating effects on natural and agriculturally important plants that rely on bumble bees as their pollinators, such as apple, almond and pear trees. Due to the importance of these pollinators in the health and maintenance of many ecologically and economically important plants, the mystery of their decline and possible solutions are a topic of much debate.

Recent reports show that, in addition to the devastating effects of habitat loss, there is pathogen spillover from the commercially reared populations, used as pollinators in greenhouses, to the natural bumble bees they come in contact with (Otterstatter & Thomson, 2008). This spillover occurs when the reservoir population, a commercial bee colony, has a highly prevalent pathogen and transmits this pathogen to a nearby alternate host, a wild population of bees. These pathogens include \textit{Crithidia bombi}, a trypanosome, and \textit{Nosema bombi}, a parasitic
fungus. Both pathogens are more prevalent in commercial populations than wild ones (Colla, Otterstatter, Gegear, & Thomson, 2006), making their spillover to native bee populations likely. With both pathogens on the rise and available habitats declining, many bumble bee species are in decline.

In an effort to predict the likely outcome of these infections and lobby for regulation of commercial bumble bees, one study tried to predict the infection rate of C. bombi from escaping commercial bees (Otterstatter & Thomson, 2008). Under their calculations, 35-100% of the wild population of bumble bees would become infected, spreading at a rate of 2km/week. Though they did see up to 47% of wild populations near the greenhouses infected, no infected bees were found farther than 6 km away from the greenhouses. This would suggest that there is an unaccounted for factor that is keeping C. bombi from infecting native populations.

The factor bringing a halt to the devastating movement of C. bombi may be the bees' intestinal microbiota. In an experimental setting, bumble bees reared in a semisterile environment were fed the feces of their nest mates and experienced significantly lower infection levels, compared to those which had little or atypical intestinal bacteria. This demonstrates that intestinal microbes shared in populations of bumble bees offer some resistance to C. bombi infection (Koch & Schmid-Hempel, 2011).

**Intestinal Microbes Promote Infection**

Though the intestinal bacteria normally found in humans are considered generally benign if not beneficial, many recent studies have shown that intestinal microbes can have a varied effect on human health, from helping prevent type 1 diabetes to causing cancer (Fox et al., 2010; King & Sarvetnick, 2011). Similarly, intestinal symbionts can be harmful to their hosts by increasing the pathogenicity of viruses, bacteria and even nematodes. Understanding how symbionts interact with one another and the effect they have on the host is crucial for the development of the host-pathogen dynamic and for the advancement of human medicine.

Basic components of bacterial cell walls and outer membranes can increase the ability of viruses to infect and replicate in mouse intestines (Kuss et al., 2011). This suggests that, even though many microbes have been documented to aid in host defense, any bacteria could be used by enteric viruses to elicit a deleterious effect on host health since the components used by the viruses are universal in bacteria. Other parasites, like the intestinal nematode Trichuris muris, use similar tactics. T. muris eggs interact directly with the surface of intestinal bacteria, using the contact as a cue for hatching (Hayes et al., 2010).

Bifidobacteria are widely considered beneficial to intestinal health for many reasons, including increased immune system stimulation (Picard et al., 2005). However, mice that experience an increase in the population of bifidobacteria exhibited a decreased resistance to Salmonella infection (Petersen et al., 2009; Petersen et al., 2010). The increased colonization of the gut with bifidobacteria was achieved by feeding the mice a particular diet, which suggests that diet manipulation can be used as a preventative measure against Salmonella and other intestinal diseases.

**Conclusion**

In order for host-pathogen models to be accurate, they must account for not only abiotic factors, but also the effects of the symbionts with which these pathogens reside.
The influence of these symbionts can vary from mild increases in pathogen resistance to substantial decreases in host defense. While it is difficult to identify all of a host's symbionts and characterize their effects, this information is valuable for future studies of pathogen virulence, as well as pathogen control plans.

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References


