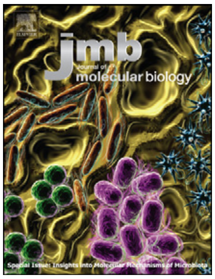

The Molecular Basis of Bacterial–Insect Symbiosis

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Abstract

Insects provide experimentally tractable and cost-effective model systems to investigate the molecular basis of animal–bacterial interactions. Recent research is revealing the central role of the insect innate immune system, especially anti-microbial peptides and reactive oxygen species, in regulating the abundance and composition of the microbiota in various insects, including *Drosophila* and the mosquitoes *Aedes* and *Anopheles*. Interactions between the immune system and microbiota are, however, bidirectional with evidence that members of the resident microbiota can promote immune function, conferring resistance to pathogens and parasites by both activation of immune effectors and production of toxins. Antagonistic and mutualistic interactions among bacteria have also been implicated as determinants of the microbiota composition, including exclusion of pathogens, but the molecular mechanisms are largely unknown. Some bacteria are crucial for insect nutrition, through provisioning of specific nutrients (e.g., B vitamins, essential amino acids) and modulation of the insect nutritional sensing and signaling pathways (e.g., insulin signaling) that regulate nutrient allocation, especially to lipid and other energy reserves. A key challenge for future research is to identify the molecular interaction between specific bacterial effectors and animal receptors, as well as to determine how these interactions translate into microbiota-dependent signaling, metabolism, and immune function in the host.

Introduction

Insects are the most successful animals, accounting for >90% of known animal species and dominating a variety of terrestrial habitats. Many insect lifestyles are founded on associations with microorganisms. These include the termites, which thrive on a diet of wood or soil through the metabolic capabilities of microorganisms in the hindgut "paunch" [1]; the leaf-cutting ants, whose apparent herbivory is based on the fungal gardens maintained in their nests [2]; and the plant sap feeding habit of many hemipterans (aphids, whiteflies, etc.), made possible by nutrient exchange with intracellular microorganisms that have been transmitted faithfully from mother to offspring for up to 100–200 million years [3]. More generally, all insects investigated to date bear resident microorganisms and, although some taxa are not obligately dependent on their microbiota, there is increasing evidence that these microorganisms influence many insect traits.

The ubiquity of microbial associations is not peculiar to insects. Rather, it is the normal condition for animals and other eukaryotes [4]. The important implication is that the capacity to interact with microorganisms has ancient evolutionary roots, even though the taxonomic composition of the microbiota can vary widely. We should therefore expect that various aspects of the signaling pathways and regulatory circuits controlling animal function have evolved, and function optimally, in the context of continual interactions with microorganisms and that the fundamental molecular principles dictating interactions with resident microorganisms are likely to be conserved across the animal kingdom. Thus, the study of insect interactions with the resident microbiota not only is of intrinsic interest but can also shed light on

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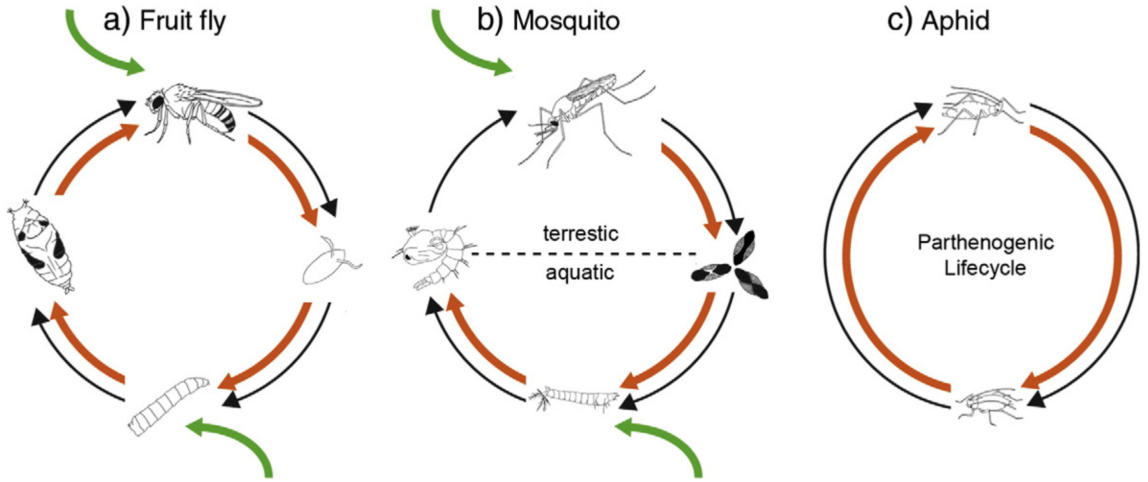

Fig. 1. Interactions between insects and resident microbiota. (a) Gut microbiota of *D. melanogaster*, an open system in which both larval and adult stages gain microorganisms from the environment and previous life stages. (b) Gut microbiota of the mosquito, comparable to *Drosophila*, except that the microbiota is not retained in the pupal stage. (c) Intracellular bacteria in the aphid, an example of a bacteriocyte symbiosis (see the text) in which the microorganisms are transmitted vertically to the female ovaries and inserted into the developing embryo; aphids have no pupal stage and summer generations (depicted) are viviparous. Black arrows, insect life stages; orange arrows, transmission of bacteria across life stages; green arrows, acquisition of microorganisms from the environment (figure prepared by S. Villareal and S. Franzenburg).

equivalent processes in other animals, including humans. In other words, just as studies on *Drosophila* and other insects have revealed the fundamental principles of many processes from embryonic development and hormone function to innate immunity and gene expression, thus, research on the relationship between insects and microorganisms has the potential to identify the basic ground rules of how animals negotiate with their resident microbiota.

This article provides an overview of recent advances in our understanding of the molecular basis of insect interactions with resident bacteria. Although these associations have been investigated from the perspectives of morphology and whole-insect physiology for many decades, it is only in recent years that the underlying molecular processes have started to be dissected. Much of the molecular research has been conducted on *Drosophila melanogaster*, but important insights have also been obtained from studies of other insect species, including mosquitoes and aphids (Fig. 1). This review addresses how the microbial populations are regulated, as well as the molecular basis of their contributions to insect nutrition and defense against natural enemies.

Regulation of the Microbial Populations Associated with Insects

The resident microbiota of insects is regulated, meaning that the abundance, composition, and location of the microorganisms fall within certain bounds. Most of the research on the molecular mechanisms that determine the abundance and composition of the insect-associated microorganisms has focused on the role of insect immunity, especially in *Drosophila* and mosquitoes. The fundamental question posed by this line of research is: How is the immune system structured, such that pathogens are generally eliminated and other microorganisms are spared? In principle, the microbial community may be dominated by taxa that are variously resistant to host immune effectors, lack immune elicitors, or trigger negative regulators of the immune response. The data are fragmentary and often contradictory, but instances of all three modes of interaction with the host immune system have been identified. The key immune effectors that have been studied are anti-microbial peptides (AMPs) and reactive oxygen species (ROS), and they are considered below.

Drosophila is an amenable system to study interactions between AMPs and the gut microbiota because the profile of AMPs and the regulation of their production are well understood. The expression of genes for two complementary sets of AMPs are induced by the IMD (*im*mune *d*eficiency) and Toll signaling pathways, with activity predominantly against Gram-negative and Gram-positive bacteria, respectively [5]. Only the IMD pathway is expressed in the midgut of the adult fly, and genetic deletion of this pathway results in a 10-fold increase in numbers