Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Insect Science

The mosquito microbiota influences vector competence for human pathogens

Nathan J Dennison, Natapong Jupatanakul and George Dimopoulos

The midgut of insect vectors of human disease contains not only pathogens harmful to human health, but also a diverse microbiota. This microbiota can influence insects' susceptibility to human pathogens, and the capacity to transmit them, through different mechanisms. Understanding the interaction between the vector, its microbiota and transmitted pathogens will provide novel opportunities to limit disease transmission.

Addresses
Harry Feinstone Department of Molecular Microbiology and Immunology, Bloomberg School of Public Health, Johns Hopkins University, 615N. Wolfe Street, Baltimore, MD 21205, USA

Corresponding author: Dimopoulos, George (gdimopo1@jhu.edu, gdimopou@jhsph.edu)

Current Opinion in Insect Science 2014, **3**:6–13

This review comes from a themed issue on **Vectors and medical and veterinary entomology**

Edited by **Julián F Hillyer**

For a complete overview see the Issue and the Editorial

Available online 1st August 2014

http://dx.doi.org/10.1016/j.cois.2014.07.004

2214–5745/© 2014 Elsevier Inc. All rights reserved.

Introduction

Mosquito vector-borne diseases such as malaria, dengue and chikungunya represent a major global public health burden. In addition to disease-causing pathogens, mosquitoes are also continuously exposed to a variety of microorganisms from their ecosystem. Some microorganisms have co-evolved and developed symbiotic relationships with insects; other bacteria are commensal, likely acquired from the insect's breeding water or nectar sources, and they have adapted to persist within the insect. Early studies of insect symbionts suggest that they nutritionally benefit the insect, as in the case of cellulose digestion by the termite's gut microbiota [1,2]. Studies also suggest the importance of the insects' microbiota in activating and maintaining its basal immune activity and immune priming [3–5]. The microbiota can modulate the mosquito immune response and influence vector competence to human pathogens. For example, the removal of the majority of midgut bacteria through antibiotic treatment results in a greater susceptibility of *Anopheles gambiae* and *Aedes aegypti* to *Plasmodium falciparum* and dengue virus (DENV) infection, respectively [6••,7••,8••]. In addition to activating mosquito immune responses, bacteria can also influence insect mosquito competence by impairing pathogen infection through competition for resources or the secretion of anti-pathogen molecules [9,10,11••].

Vector-borne disease transmission requires successful interactions between the human host, the pathogen, and the insect vector. Although the majority of research aimed at vector-borne disease control has thus far focused on the interactions between human and pathogen (i.e. vaccine and drug development), or between human and vector (i.e. insecticide development), the insect–pathogen interaction has evolved into a major area of study as we attempt to understand the importance of the tripartite interaction between vector, pathogen, and microbiota for disease transmission. This review will focus on recent advances in our understanding of the role of the mosquito microbiota in modulating infections with vector-borne pathogens, which could lead to alternative disease control strategies.

Mosquito immune responses to pathogens

In order to fight invading pathogens, insects mainly rely on their innate immune systems, which are to a significant degree controlled through different immune signaling cascades. Following recognition of pathogens through pattern recognition receptors (PRRs), immune pathway activation results in the systemic production of antimicrobial peptides (AMPs) and other anti-pathogen immune effectors, as well as other immune defense mechanisms such as melanization and phagocytosis [12–19]. Our current knowledge of insect immune signaling pathways is mainly based on research in *Drosophila* and mosquito models (reviewed in [20–22]). Classical immune pathways in insects, namely the Toll, immune deficiency (Imd), and Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways, are activated in response to wide range of pathogens. The Toll pathway, an insect NF-kB signaling pathway, is mainly activated by Gram-positive bacteria, fungi, and viruses [6••,23–28]. Another NF-kB signaling pathway, the Imd pathway, plays an important role in the insects' immune responses to bacteria, viruses, and the human *Plasmodium* parasite *P. falciparum* [29–32]. The insect

JAK/STAT pathway is analogous to the vertebrate interferon (cytokine)-induced signaling pathway and has been shown to mediate insect anti-viral immunity as well as the mosquito defense against bacteria, fungi, and *Plasmodium* parasites [33–43]. Given the extensive overlap between the antibacterial, anti-parasitic, and antiviral immune responses, the microbiota can act through the immune system as a key determinant of vector susceptibility to human pathogen infection [6••,7••,44••,45•].

Microbial components such as peptidoglycan (PGN) can establish basal immunity and induce genes with cross-reactivity against both bacteria and *Plasmodium* parasites [7••,44••]. Following ingestion of a blood meal, the bacterial population can expand 100-fold, and the transmembrane PGN recognition protein LC (PGRPLC) acts as a sensor for recognition of both Gram-negative and Gram-positive bacteria and subsequent expression of AMPs [46•,47,48•]. Depletion of PGRPLC results in a bacteria-dependent increase in *Plasmodium* infection levels, suggesting that the presence of bacteria is essential for the PGRPLC-mediated anti-*Plasmodium* immune response [48•]. Other PRRs, the C-type lectins CTL4 and CTLMA2, have pleiotropic immune functions, acting as protective agonists preventing *P. berghei* melanization and regulating susceptibility to Gram-negative bacteria [49,50]. Shared immune signaling in response to different classes of microorganisms dictates that the presence, and likely the composition, of the microbiota influence susceptibility to human pathogen infection.

Mosquito microbiota influences vector competence

The insect's microbial symbionts reside in various organs such as the gut, ovaries, Malpighian tubules, and hemocoel [51]. The gut microbiota is of particular interest because it represents the first site of most extensive exposure to pathogens. Insect gut microbiomes, especially those of mosquitoes, have been characterized by either classical cultivation methods or by metagenomic analyses based on 16S rRNA sequencing [52–57]. The bacterial composition of mosquitoes sampled from natural habitats is highly variable but often contain a core microbiome that is dominated by a small number of taxa that can, however, vary depending on the insect species, geographical origin, ecological niche, and source of food, as well as sex [52–54,56]. Members of the Proteobacteria class are often the most abundant and common in adult *A. gambiae* mosquitoes, with species of the *Enterobacter*, *Serratia*, and *Asaia* genera commonly present [11••,52,53]. Interestingly, the microbiota of immature stages is mainly comprised of *Cyanobacteria*, suggesting a shift in microbial communities occurs as the midgut ecosystem changes during development [58]. Despite their core microbiota, a high inter-individual variation in bacterial species composition is frequently found, even within the same mosquito colony and generation [7••,52], suggesting that the midgut is predominantly composed of opportunistic bacteria that can tolerate the protease-rich restrictive environment.

An inverse correlation exists between the presence of certain Gram-negative bacteria in mosquitoes and *P. falciparum* infection rates, and several bacterial species have been shown to inhibit *Plasmodium* sporogonic development *in vivo* and *in vitro* [46•,59••,60••,61••]. Antibodies targeting Gram-negative bacteria within the mosquito midgut increase permissiveness to *Plasmodium* infection [62], and removal of *Ae. aegypti* endogenous bacteria results in an increased susceptibility to DENV infection [6••]. Reintroduction of certain field-derived bacteria into the mosquito gut through a nectar meal increases the resistance to pathogen infection in both *A. gambiae* [46•] and *Ae. aegypti* [45•], although not all bacteria tested influence the susceptibility to infection. Our knowledge of the precise mechanisms by which certain bacteria can influence the mosquitoes' susceptibility to human pathogens is still limited. Below, we detail the multiple mechanisms through which the insect vector microbiota is likely to influence susceptibility to pathogens and summarize these effects in Table 1.

Resource competition

Both bacterial symbionts and pathogens acquire certain essential nutrients from their insect hosts. *Plasmodium* oocysts internalize the mosquito lipoprotein lipophorin, suggesting a metabolic demand for vector-derived lipids [63]. Intracellular membrane remodeling is important for efficient virus replication and protein processing of DENV and WNV [64,65]. To modulate host membrane trafficking, DENV influences lipid composition, lipid homeostasis and genes involved in lipid trafficking in both vertebrate and invertebrate model [66–68]. Chemical inhibition of fatty acid synthase enzyme inhibited DENV, emphasizing the importance of lipids in virus replication [66,69]. Similar to chemical treatment, the presence of symbionts can sequester such nutrients and thereby limit the development and infection of pathogens. For example, it is suggested that *Wolbachia*, the most prevalent intracellular symbiont of insects, sequesters cholesterol and other lipids in insect cells, and depletion of these lipids, in turn, limit infections with DENV, Chikungunya virus (CHIKV), and the *Plasmodium* parasite [9,70]. Abundance of cholesterol mitigates the *Wolbachia* inhibition of *Drosophila* C Virus, further suggesting that resource competition can contribute to pathogen resistance [71].

Immune priming by the microbiota

There is growing evidence for the importance of the insect microbiota for immune activation and maturation, ensuring that a robust anti-parasitic response occurs in adulthood. Gene expression analysis has revealed that aseptic *A. gambiae* and *Ae. aegypti* have lower levels of immune gene expression [6••,7••]. This finding, in

Download English Version:

https://daneshyari.com/en/article/4508270

Download Persian Version:

https://daneshyari.com/article/4508270

Daneshyari.com