PLOS ONE

Complex Modulation of the *Aedes aegypti* Transcriptome in Response to Dengue Virus Infection

Mariangela Bonizzoni, W. Augustine Dunn, Corey L. Campbell, Ken E. Olson, Osvaldo Marinotti, Anthony A. James

Published: November 27, 2012 • DOI: 10.1371/journal.pone.0050512

Abstract

Dengue fever is the most important arboviral disease world-wide, with *Aedes aegypti* being the major vector. Interactions between the mosquito host and dengue viruses (DENV) are complex and vector competence varies among geographically-distinct *Ae. aegypti* populations. Additionally, dengue is caused by four antigenically-distinct viral serotypes (DENV1–4), each with multiple genotypes. Each virus genotype interacts differently with vertebrate and invertebrate hosts. Analyses of alterations in mosquito transcriptional profiles during DENV infection are expected to provide the basis for identifying networks of genes involved in responses to viruses and contribute to the molecular-genetic understanding of vector competence. In addition, this knowledge is anticipated to support the development of novel disease-control strategies. RNA-seq technology was used to assess genome-wide changes in transcript abundance at 1, 4 and 14 days following DENV2 infection in carcasses, midguts and salivary glands of the *Ae. aegypti* Chetumal strain. DENV2 affected the expression of 397 *Ae. aegypti* genes, most of which were down-regulated by viral infection. Differential accumulation of transcripts was mainly tissue- and time-specific. Comparisons of our data with other published reports reveal conservation of functional classes, but limited concordance of specific mosquito genes responsive to DENV2 infection. These results indicate the necessity of additional studies of mosquito-DENV interactions, specifically those focused on recently-derived mosquito strains with multiple dengue virus serotypes and genotypes.

Figures

Citation: Bonizzoni M, Dunn WA, Campbell CL, Olson KE, Marinotti O, et al. (2012) Complex Modulation of the *Aedes aegypti* Transcriptome in Response to Dengue Virus Infection. PLoS ONE 7(11): e50512. doi:10.1371/journal.pone.0050512

Editor: Luciano A. Moreira, Centro de Pesquisas René Rachou, Brazil

Received: July 5, 2012; **Accepted:** October 22, 2012; **Published:** November 27, 2012

Funding: This work was supported by grant U54AI065359 from the National Institute of Allergy and Infectious Diseases. WAD is supported in part by T15LM07443 from the National Library of Medicine, United States National Institutes of Health (NIH). C.L. Campbell and K.E. Olson are supported in part by a grant to the Regents of the University of California from the Foundation for the NIH through the Grand Challenges in Global Health initiative. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Introduction

The World Health Organization lists dengue as the most important arthropod-borne viral disease of humans [1]. The major vector of all four dengue virus serotypes (DENV1–4) is the cosmopolitan mosquito, *Aedes aegypti*. Close association with human populations and increasing intercontinental travel favor the expansion of its geographic distribution. There are no effective prophylactic and therapeutic drugs specific for dengue, and vaccine development is hindered by potential antibody-dependent enhancement that could put people at greater risk of life-threatening, severe dengue [2]. As a consequence, vector control is currently the only practical and effective strategy for disease prevention. The *Ae. aegypti* genome was sequenced and knowledge of genome-wide changes in patterns of gene expression following DENV infection is expected to identify genes involved in vector competence, the intrinsic ability of the mosquito to host and transmit DENV [3], [4]. This knowledge, coupled with germline transformation technology and anti-viral effector molecules, can be applied to the development of genetically-modified mosquitoes incapable of arbovirus transmission [5]–[7].

Although vertical transmission of dengue viruses has been reported, mosquitoes become infected mainly following ingestion of an infectious-blood meal [8], [9]. Viruses are transmitted to new human hosts during a subsequent bloodmeal following an extrinsic incubation period (EIP) of 7–14 days. The duration of the EIP depends on the mosquito strain, virus genotype and environmental factors [10]–[14]. During the first 1–2 days post infection (dpi), DENVs invade midgut epithelial cells through receptor-mediated endocytosis and initiate replication [15]–[18]. These processes involve both viral and host cellular factors [19]. Infection spreads laterally in the midgut epithelium to cells adjacent to those infected originally [13]. Virus titers peak in the midgut usually between 7–10 dpi and are followed by a decline [13], [20]. DENV infection disseminates from the midgut throughout the body, presumably through the tracheal system, reaching the salivary glands as early as 3 dpi [13]. Maximum virus titers in the salivary glands are reached 12–18 dpi. The saliva of an infected mosquito containing DENVs is injected in a human host during feeding to complete the transmission cycle.

Aedes aegypti populations of different geographic origin vary in their vector competence. Phenotypes include those in which DENVs either cannot establish a midgut infection (Midgut Infection Barrier) or cannot disseminate to other tissues (Midgut Escape Barrier) [11], [21], [22]. Other phenotypes manifest in the absence of virions in the saliva (Transmission Barrier). Differences in intensity of infection (peak titers) and duration of EIP also are observed among mosquito strains [13].