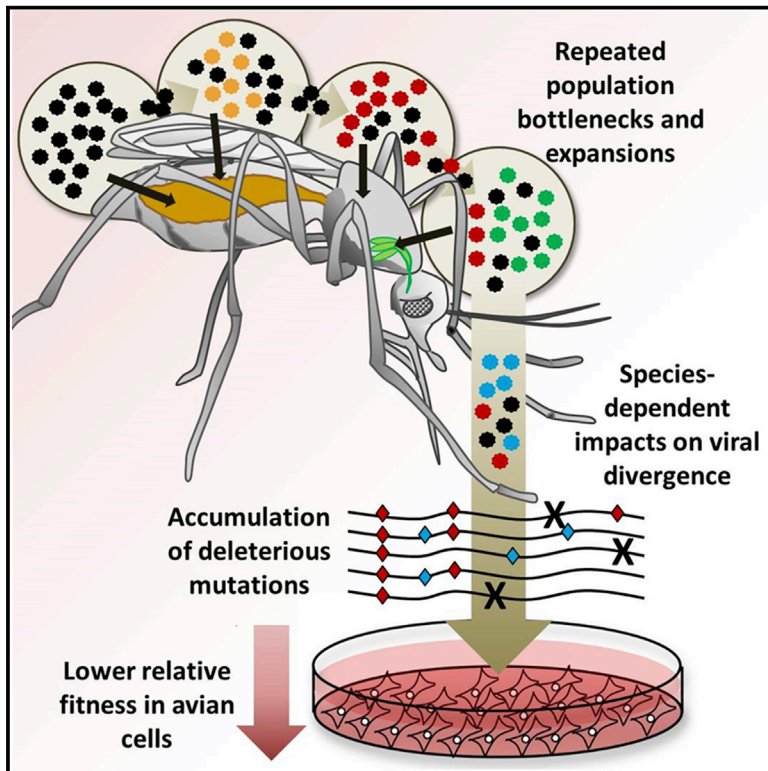


Cell Host & Microbe

Genetic Drift during Systemic Arbovirus Infection of Mosquito Vectors Leads to Decreased Relative Fitness during Host Switching

Graphical Abstract



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In Brief

Mosquito-borne viruses must adapt to different vectors and hosts to sustain transmission. Grubaugh et al. reveal that viruses undergo repeated tissue-associated bottlenecks during systemic mosquito infection, and the recovery of genetic diversity is species dependent. These cycles, along with weak purifying selection, are responsible for the fitness costs associated with mosquito transmission.

Highlights

- Mosquito species differentially affect West Nile virus evolution upon systemic infection
- Tissue-associated bottlenecks cause repeated stochastic reductions in genetic diversity
- Weak purifying selection leads to the accumulation of deleterious mutations
- Mosquito transmission imposes fitness costs on viruses during vertebrate infection



Genetic Drift during Systemic Arbovirus Infection of Mosquito Vectors Leads to Decreased Relative Fitness during Host Switching

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SUMMARY

The emergence of mosquito-borne RNA viruses, such as West Nile virus (WNV), is facilitated by genetically complex virus populations within hosts. Here, we determine whether WNV enzootic (*Culex tarsalis*, *Cx. quinquefasciatus*, and *Cx. pipiens*) and bridge vectors (*Aedes aegypti*) have differential impacts on viral mutational diversity and fitness. During systemic mosquito infection, WNV faced stochastic reductions in genetic diversity that rapidly was recovered during intra-tissue population expansions. Interestingly, this intrahost selection and diversification was mosquito species dependent with *Cx. tarsalis* and *Cx. quinquefasciatus* exhibiting greater WNV divergence. However, recovered viral populations contained a preponderance of potentially deleterious mutations (i.e., high mutational load) and had lower relative fitness in avian cells compared to input virus. These findings demonstrate that the adaptive potential associated with mosquito transmission varies depending on the mosquito species and carries a significant fitness cost in vertebrates.

INTRODUCTION

The emergence of arthropod-borne RNA viruses (arboviruses) is an ongoing problem that imposes significant health and economic burdens on communities worldwide. West Nile (WNV), chikungunya (CHIKV), dengue (DENV), and Zika viruses are all in various states of emergence at local or global scales (Kramer et al., 2008; Lanciotti and Valadere, 2014; Musso et al., 2015). The mechanisms underlying arbovirus emergence are complex and include, for example, altered land use and increased global travel. In addition, RNA viruses have an inherent ability to rapidly mutate and thus generate opportunities for adaptation in novel environments through an error-prone polymerase (Holland et al., 1982). WNV is an excellent example of an introduced RNA virus that adapted to a new environment (i.e., new genotype

linked to a shorter extrinsic incubation period in local mosquitoes), promoting its spread throughout the Americas (Moudy et al., 2007). Several studies have assessed how different host types impact WNV population structure and have shown that WNV populations are more diverse in mosquitoes compared to birds (Grubaugh et al., 2015; Jerzak et al., 2005, 2007). In mosquitoes, purifying selection is weak and virus diversification is driven by the action of RNAi, which creates an intracellular milieu that favors rare genotypes (Brackney et al., 2009; Brackney et al., 2015). In contrast, purifying selection in birds is strong (Jerzak et al., 2008) and the innate antiviral responses are dominated by type I interferon. Thus, in the WNV system, mosquitoes and birds have distinct impacts on virus population biology: Mosquitoes allow for increased adaptive plasticity, while birds maintain high fitness through purifying selection (Deardorff et al., 2011).

A wide array of studies has suggested that arboviruses can adapt to microhabitat-specific conditions. CHIKV is capable of adapting to transmission by *Aedes albopictus* during a single round of infection (Stapleford et al., 2014). WNV evolutionary dynamics have been shown to vary in response to environmental conditions (Bertolotti et al., 2008). Indeed, different avian hosts of WNV have distinct impacts on virus population structure and fitness (Grubaugh et al., 2015). The impacts of different mosquito species on WNV population biology and fitness, however, have not been directly addressed. This is a critical shortcoming in the field because throughout its distribution, WNV is maintained in its enzootic cycle by several *Culex* species, including *Culex tarsalis*, *Cx. pipiens quinquefasciatus*, and *Cx. pipiens pipiens* (Kramer et al., 2008). In addition, mosquitoes of several divergent genera have been found infected and/or demonstrated to be competent vectors (Bernard et al., 2001; Turell et al., 2005). These include *Aedes* mosquitoes that may act as a “bridge” between enzootic cycles and mammals, including humans (Kilpatrick et al., 2005). Although it seems clear that infection of mosquitoes leads to genetically complex virus populations (Jerzak et al., 2008; Sim et al., 2015; Stapleford et al., 2014), the impact of any particular mosquito species on WNV population biology has not been determined. In addition, the full range of selective forces acting on WNV during systemic infection of mosquitoes is poorly understood, and important inconsistencies persist in the literature. For example, whereas some studies have documented the existence of population bottlenecks during

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