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Abstract:

One of the defining features of mosquito vectors of arboviruses such as Dengue and Zika is their ability to tolerate high levels of virus proliferation without suffering significant pathology. This adaptation is central to vector competence and disease spread. The molecular mechanisms, pathways, cellular and metabolic adaptations responsible for mosquito disease tolerance are still largely unknown and may represent effective ways to control mosquito populations and prevent arboviral diseases. In this review article, we describe the key link between disease tolerance and pathogen transmission, and how vector control methods may benefit by focusing efforts on dissecting the mechanisms underlying mosquito tolerance of arboviral infections. We briefly review recent work investigating tolerance mechanisms in other insects, describe the state of the art regarding the mechanisms of disease tolerance in mosquitos, and highlight the emerging role of gut microbiota in mosquito immunity and disease tolerance.

Keywords: mosquito; arbovirus; disease-tolerance.

Introduction:

Diseases caused by mosquito-borne arboviruses like Dengue, Zika, Chikungunya, Yellow Fever, West Nile (WNV), Mayaro and Japanese Encephalitis (JEV), are important sources of worldwide morbidity and mortality. Dengue fever alone affects more than 390 million people every year in tropical and sub-tropical areas of the world (Bhatt et al. 2013). In the absence of an efficient vaccine, and faced with the emergence of insecticide resistant mosquito strains, it is important to explore alternative avenues of vector control. One approach is to focus on the behavioral and physiological determinants of vectorial competence, including how mosquitoes maintain homeostasis and fitness while infected with arbovirus, and how this trait influences disease transmission. If we understand what makes a good vector, we may begin to uncover new ways to reduce or even disrupt vectorial capacity.

A fundamental feature of mosquito–virus interactions is that following the ingestion of an infectious blood meal there is proliferation and spread of virus particles from the mosquito midgut to the salivary glands. During this process, mosquitoes often experience minimal physiological and fitness costs associated with arbovirus replication (Moreno-Garcia et al., 2014; Shaw et al., 2018), highlighting how mosquito vectors are tolerant to arbovirus infection (Lambrechts and Saleh, 2019). Although some work has reported different degrees of fitness costs to mosquitoes during arbovirus infection (Lambrechts and Scott, 2009; Grubaugh et al., 2017; Petersen et al., 2018; Silveira et al., 2018), virus proliferation is frequently non-pathogenic and the observed harm is host and pathogen strain-specific (Martin et al., 2010; Reiskind et al., 2010; Tesla et al., 2018; Sirisena et al., 2018).

Disease tolerance is a host defense strategy to maximize homeostasis and fitness independent of mechanisms that kill microbes. It acts in concert with other evolutionary conserved defensive strategies, such as immune resistance (killing microbes) and behavioral avoidance (reducing the risk of infection). The ability to tolerate a viral infection is no doubt an essential attribute of an effective disease vector. Given the prevalence of insect-vectored human pathogens, it is striking that we currently know so little about how mosquitos are able to tolerate infection by

the viruses they vector, and how this ability varies in natural mosquito populations (Dharmarajan et al., 2019). By understanding the metabolic and molecular mechanisms that promote disease tolerance in mosquitoes, we may uncover novel targets to reduce vector competence and block virus transmission to humans.

The link between tolerance and transmission:

Organisms have evolved a variety of behavioral and physiological strategies to avoid, clear or tolerate infections. Immune-mediated pathogen killing is a well-studied strategy that contributes to disease resistance. Acting independently or in cooperation with mechanisms that kill pathogens, immune-metabolic and physiological responses to infection may also promote tissue protection or repair, preserving host homeostasis during infection (Martins et al., 2019; Ganeshan et al., 2019). These responses secure host health and recovery independently of pathogen killing, and so they are likely to promote disease tolerance, allowing hosts to maintain a relative level of health despite harboring relatively high pathogen burdens (see Box 1). The concept of health is directly connected to homeostasis and the ability to maintain animal physiologies operating properly at the cellular, tissue and systemic levels (Buchman , 2002; Chovatiya and Medzhitov, 2014).

While disease tolerance may improve host health at the individual level, because infectious hosts remain alive and healthy for longer, one potential population-level consequence of elevated disease tolerance is an increase in the prevalence of infection (Miller et al., 2005; Read et al., 2008; Vale et al., 2014). Beyond this intuitive reasoning, there is evidence from both theoretical and experimental approaches that reducing the severity of disease in the host (increasing disease tolerance) can lead to increased spread and prevalence of infection (Hozé et al., 2018; Read et al., 2015; Vale et al., 2014). For example, environmental conditions conducive to greater disease tolerance have been found to foster super-shedding individuals who contribute disproportionately more to the total transmission (Vale et al., 2013, 2011), while therapeutic interventions that boost host tolerance are predicted to increase the prevalence of infections (Hozé et al., 2018; Vale et al., 2014), mainly through the impact of increasing host lifespan,

and consequently, the infectious period. To fully grasp the consequences of disease tolerance for pathogen spread, it is therefore important to quantify the extent of natural variation in infection tolerance, and test if more tolerant individuals have greater potential for disease transmission (Henschen and Adelman, 2019; Vale et al., 2013).

How do organisms tolerate infection?

Understanding the physiological mechanisms underlying disease tolerance phenotypes in mosquitos would be helpful in designing therapeutic interventions that aim to reduce their tolerance to vectored pathogens as a means of reducing their vectorial competence (Shaw et al., 2018). The most obvious candidates for such mechanisms are those which either prevent tissue damage from occurring or that are central in the process of repairing tissue damage (Martins et al., 2019; Soares et al., 2017, 2014). Mechanisms that target secreted virulence factors or toxins, for example, are good candidates for tolerance mechanisms because they can prevent pathology without directly eliminating pathogens (Allen et al., 2014; Rasko and Sperandio, 2010; Vale et al., 2014). Disease severity is also directly affected by immunopathology induced during prolonged or unregulated inflammatory responses to pathogens, and therefore anti-inflammatory mechanisms are equally promising mechanisms of disease tolerance (Ayres and Schneider, 2012; Martins et al., 2019; Vale et al., 2014). Finally, once damage has occurred, more tolerant hosts are likely to repair tissue damage and recover from infection. Our understanding of how mosquito vectors tolerate infection would therefore be greatly enhanced by focusing our efforts on mechanisms that promote physiological integrity, reduced inflammation and enhanced tissue damage repair. However, we currently have a limited understanding of the physiological and immune mechanisms that allow arthropod vectors to tolerate infection. Since arbovirus infection and transmission by mosquitoes are closely associated with hematophagy, the metabolic adaptations triggered by the pro-oxidant nature of the blood meal (Sterkel et al., 2017) are likely to modulate mosquito disease tolerance to arbovirus.

What can other insects teach us about disease tolerance mechanisms in mosquito vectors?

Disease tolerance has been well studied in plants (Baucom and de Roode 2011) and more recently in animals (Råberg et al. 2009; Ayres and Schneider 2008; Baucom and de Roode 2011; Vale and Little 2012). In invertebrates, most research has focused on bacterial or viral infections in *Drosophila* (Brandt et al. 2004; Ayres and Schneider 2008; Teixeira 2012) or bacterial infections in the freshwater crustacean *Daphnia* (Vale et al. 2011; Vale and Little 2012), and protozoan infections in Monarch butterflies (Lefèvre et al. 2011; Sternberg et al. 2013). Despite the obvious differences between the physiology of hematophagous vectors and other ecologically distinct hosts, there is substantial evolutionary conservation in immune and tissue repair mechanisms that mediate the response to many infections (Hoffmann et al., 1999). One potentially helpful approach may therefore be to leverage work done in other model systems of infection, particularly insects, to identify potential candidate mechanisms of disease tolerance in mosquito vectors (Gupta and Vale, 2017; Howick and Lazzaro, 2014; Lissner and Schneider, 2018; Louie et al., 2016; Sternberg et al., 2012; Troha et al., 2018).

For example, a recent comparison of transcriptional profiles in Drosophila infected with a range of bacterial pathogens identified the transcription factor CrebA which, when knocked down, resulted in reduced tolerance due to increased cellular stress (Troha et al., 2018). Other work in Drosophila measured tolerance to bacterial infection in a panel of inbred lines and identified several candidate genes associated with variation in disease tolerance (Howick and Lazzaro, 2017). Among them, *grainy head* (*ghd*) is shown to be involved in epithelial would repair via embryonic ERK pathway signaling, and *debris buster* (*dsb*) is previously implicated in autophagy of cellular debris (Han et al., 2014; Howick and Lazzaro, 2017; Mace et al., 2005). These two studies highlight that the maintenance of cellular homeostasis in addition to tissue damage repair may be central to disease tolerance in insects.

Other work in Drosophila has also shed light on how immune regulation mechanisms may play an important role in disease tolerance. The epigenetic regulator of the JAK-STAT pathway G9a, for example, has been identified as being

important in tolerating systemic infection by Drosophila C Virus, mainly due its role in downregulating immunopathology during viral infection (Merkling et al., 2015). Interestingly, G9a appears to have greater effects in male flies, and affects tolerance not by reducing the overall severity of infection, but by changing the sensitivity of flies to increasing concentrations of DCV (Gupta and Vale, 2017). Future work may therefore benefit from focusing on negative regulators of immune responses as key mediators of disease tolerance.

Mechanisms of disease tolerance to arbovirus infection in mosquitoes:

Several immune signaling pathways are activated in mosquitoes during arboviral infections, such as the antiviral RNAi (Sanchez-Vargas et al., 2009; Olmo et al., 2018), JAK-STAT (Souza-Neto et al., 2009), Toll (Xi et al., 2008), and IMD (Barletta et al., 2017) pathways. The inhibition of specific components of immune resistance, such as RNAi, leads to viral over proliferation and host mortality, demonstrating that controlling viral growth is essential for mosquito defense (Myles et al., 2008; Cirimotich et al., 2009). Despite that, antiviral immune resistance operates at low to moderate levels. Arbovirus titers increase 100 to 1000-fold in mosquito bodies following an infectious blood meal and Dengue, for example, can establish persistent lifelong infections (Salazar et al., 2007). This lower state of immune resistance maintains viral burden under an acceptable homeostatic range for the vector, but is only possible because mosquitoes rely on complementary defensive strategies that prevent arbovirus-triggered pathology. Below, we briefly describe some known mechanisms involved in vector disease tolerance, including the role of gut microbiota in the modulation of vector competence (Box 2).

Cellular renewal and homeostasis. Cell death and regeneration determine disease tolerance in different systems through the modulation of tissue composition and integrity (Jamieson et al., 2013; Sahoo et al., 2014; Soares et al., 2017). In mosquitoes, apoptosis impacts vector competence leading to antagonistic outcomes depending on arbovirus and insect species. *Aedes aegypti* strains refractory to Dengue have increased expression of pro-apoptotic genes and higher numbers of midgut apoptotic cells during infection (Ocampo et al., 2013, Eng et al., 2016) and

187 the induction of apoptosis controls Sindbis spread, collectively suggesting mosquito
188 cell death can restrict arbovirus (O'Neill et al., 2015). Paradoxically, inhibiting
189 apoptosis through silencing of the initiator caspase Aedronc decreased Dengue virus
190 load and dissemination (Eng et al., 2016) and activating apoptosis using RNAi-
191 mediated silencing of the anti-apoptotic gene iap1 increased Sindbis infection
192 (Wang et al., 2012). To compensate for the loss of apoptotic cells that could
193 compromise tissue integrity, damage caused by chemical or infectious insults trigger
194 an adaptive response leading to cell regeneration and reestablishment of midgut
195 homeostasis (Janeh et al., 2017). In the context of Dengue infection, the proliferation
196 of intestinal stem cells (ISC) is delayed in susceptible *A. aegypti* Rockefeller strain,
197 suggesting that midgut cell renewal may regulate vector competence (Taracena et
198 al., 2018). So far, it is not clear how cell turnover influences mosquito-virus
199 interactions and we can only speculate that the interplay between infection-induced
200 apoptosis and the compensatory ISC proliferation is likely to contribute to tissue
201 integrity, midgut homeostasis and vector disease tolerance. In a recent study,
202 Thaker and collaborators (2019) compared metabolic alterations induced by Zika in
203 mosquito versus human cell and revealed an energy depletion that led to AMPK
204 activation and apoptosis in humans but not mosquito cells, which, if confirmed in
205 whole insects, could help to explain the tolerance phenotype of infected mosquitoes
206 (Figure 2).

207 *Reducing viral pathology.* The neutralization of arbovirus-induced pathology
208 in mosquitoes is essential for disease transmission. Some flavivirus, such as Dengue
209 and Zika, show neurotropism for mosquito nervous system, including the brain, and
210 promote behavioral alteration in infected females (Zhang et al., 2010; Lima-Camara
211 et al., 2011; Gaburro et al., 2018). The neural factor Hikaru genki of *A. aegypti*
212 (AeHig) is expressed in the nervous system and promotes disease tolerance by
213 restricting neuronal apoptosis and arbovirus damage to mosquito brains,
214 preventing lethal infections following arbovirus-contaminated blood meals (Xiau et
215 al., 2015).

216 *Modulation of arboviral persistent infections*: Insect cells and mosquitoes
217 infected with arbovirus, such as Dengue, Chikungunya, Zika and West Nile, produce

viral DNA fragments (vDNA) that integrate into mosquito genomes, known as endogenous viral elements (EVEs) (Crochu et al., 2004, Nag et al., 2016 and 2017). vDNA synthesis is mediated by the reverse transcriptase activity of mosquito transposons, uses defective viral genomes as templates and is modulated by Dicer-2 (Poirier et al., 2018). EVEs can be either incomplete or contain functional open reading frames of several arbovirus (Suzuki et al 2017; Palatini et al., 2017) inserted into a genomic loci rich in transposable elements called piRNA clusters (Arensburger et al., 2011; Whitfield et al., 2017). Transcripts derived from EVEs inserted into piRNA clusters activate the piRNA pathway, which is expanded in *Aedes* mosquitoes, to generate virus-derived piRNAs (vpiRNAs) that contribute to mosquito antiviral resistance (Morazzani et al., 2012; Schnettler et al., 2013; Miesen et al., 2015; Miesen et al., 2016). vDNA also mediates persistent viral infections in mosquitoes, potentially connecting its synthesis to vector disease tolerance (Goic et al., 2016) (Figure 2). *Aedes albopictus* infected with Chikungunya and treated with AZT, an inhibitor of reverse transcriptase, had reduced vDNA levels and increased vector mortality following infection without alterations in viral loads, suggesting that arboviral disease tolerance is dependent on the formation of vDNA (Goic et al., 2016). How vDNA is involved in the establishment of viral persistent infections and vector disease tolerance awaits further investigations.

Conclusion and perspectives:

After feeding on virus-contaminated blood, vector mosquitoes support intense virus proliferation without major homeostatic imbalances, being tolerant to arbovirus. Targeting tolerance-promoting pathways have the potential to decrease vector competence due to reduction in mosquito health and fitness, ultimately affecting the number of infectious bites and/or vector lifespan. By learning how mosquitoes tolerate infection we may uncover potential therapeutic targets to inhibit vector tolerance, inducing mosquito mortality and disrupting arbovirus transmission.

Box 1 - Measuring tolerance: the relationship between health and pathogen load

When comparing two different groups or populations of hosts, a common approach is to analyze how host health changes with increasing infection loads for each of the groups of interest (Raberg et al., 2007). In its simplest form, this relationship may be linear, and host groups showing steep negative slopes for this reaction norm suffer a loss in health with increasing loads, while hosts with flat reaction norms are able to maintain health even as pathogen loads increase, and are therefore relatively tolerant (Figure 1a).

Depending on the nature of the data, more complex non-linear relationships are also possible, as has been shown in viral and bacterial infections in *Drosophila* (Gupta and Vale, 2017; Howick and Lazzaro, 2014; Louie et al., 2016) and in HIV infection in humans (Regoes et al., 2014). In these cases, a non-linear logistic model may be more appropriate (Figure 1b). This type of model goes beyond the analysis of the rate of health loss with increasing pathogen loads, providing information about how groups of hosts may differ in various parameters of the response to infection, including their vigor in the absence of infection, sensitivity to increases in pathogen load (affecting the lethal load of infection) or the severity of infection, which determines how sick a host can get during infection, including ultimate death (Figure 1b) (Louie et al., 2016).

An important consideration in both linear and non-linear analyses is that they require both health and pathogen load to be measured on the same individuals (each data-point in the correlation must correspond to one individual host). This is often not possible when obtaining these data since it requires destructive sampling of the individual host, which is often the case in mosquitos and other invertebrates. In these cases, it is still possible to measure tolerance as the average health of a group of hosts relative to the average pathogen load of the same group (Figure 1c). For example, genotype-specific measures of survival and pathogen loads could be useful to distinguish differences in tolerance among distinct genetic backgrounds of mosquito, even if survival and pathogen loads are measured in different groups of insects.

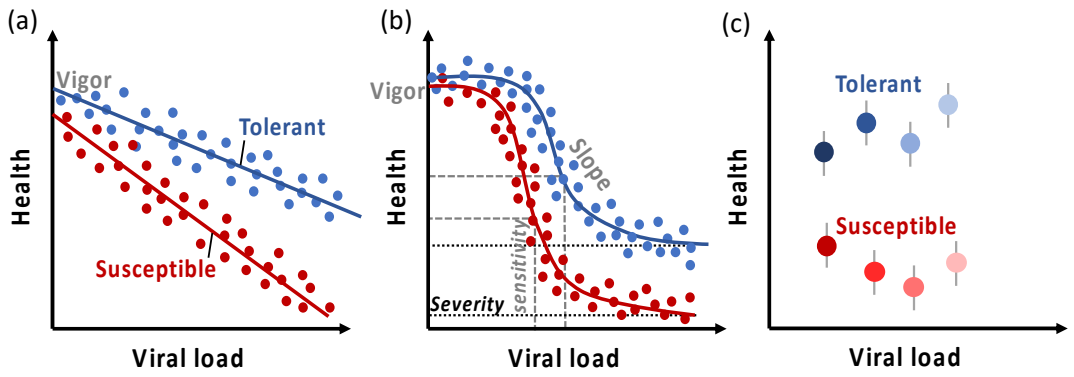

Figure 1: A tolerance curve is a tool to quantify disease tolerance in distinct populations. The shape of tolerance curves allows distinct interpretations of host – pathogen interactions: (a) In linear tolerance curves it is possible to measure vigor (health of uninfected individuals) and the slope of health loss over an infectious gradient. However, the relationship between host health and pathogen load is often not best described by a linear model, and using a sigmoid model as seen in (b) with the 4-parameter logistic model (vigor, slope, sensitivity and severity) allows a better analysis of infection dynamics. (c) "Point tolerance" describes different tolerance properties of populations where health and viral loads were measured in distinct pools of infected hosts.

Box 2 – Gut microbiota and the modulation of vector competence

The intestinal microbiota of insects plays an important role in several host processes, including gut cell renewal and growth (Buchon et al., 2009; Shin et al., 2011); nutrient breakdown and supplementation (Warnecke et al., 2007; Hongoh et al., 2008; Nikoh et al., 2011) and toxin catabolism, among others (Kikuchi et al., 2012; Ping et al., 2007). Given its profound relationship with host physiology, it is likely that vector microbiota also modulates disease tolerance, as shown in non-insect models (Ripert et al., 2016; Rangan et al., 2016; Ayres, 2016). In the following paragraphs, we discuss how the microbiota influences pathogen colonization and vector competence by enhancing or inhibiting the presence of gut pathogens.

The composition of the vector's intestinal microbiota is fundamental in regard to its ability (competence) to transmit pathogens to humans (Ramirez et al. 2014, Bahia et al., 2014). This was illustrated in studies with *Anopheles gambiae* and *A. aegypti* where the removal of bacteria from the insect's midguts with antibiotics increased parasitemia with *Plasmodium* spp. and dengue virus (Dong et al., 2009; Xi et al., 2008) through different mechanisms (Saraiva et al., 2016). The microbiota shapes peritrophic matrix formation and influences innate immune system activation (Rodgers et al., 2017). The microbiota proliferation after blood meal induces the IMD immune pathway and antagonizes virus infection (Barletta et al., 2017). The caudal transcription factor, a negative regulator of IMD, facilitates microbiota tolerance by down-regulating REL2-dependent expression of antimicrobial peptides, specifically in the gut, thereby enabling microbiota establishment (Clayton et al., 2013).

The insects´ gut *Enterobacter* sp. bacterium secretes reactive oxygen species that kills *Plasmodium* in the gut lumen of *Anopheles* mosquitoes (Cirimotich et al., 2011). *Chromobacterium* sp. secretes a neutral protease and an aminopeptidase that degrade the viral envelope (E) protein and thus inhibit viral attachment and subsequent infection of *A. aegypti* cells (Ramirez et al., 2014; Saraiva et al., 2018a). The *Chromobacterium* sp. also has *in vivo* and *in vitro* anti-*Plasmodium* properties through secretion of romidepsin (Ramirez et al., 2014; Saraiva et al., 2018b).

By contrast, the microbiota may instead facilitate pathogen replication. The susceptibility of *A. aegypti* to Dengue virus infection increases significantly after *Serratia odorifera* gut colonization (Apte-Deshpande et al., 2012). Similarly, the *Penicillium chrysogenum* fungus makes *A. gambiae* more susceptible to *Plasmodium* infection through the upregulation of mosquito ornithine decarboxylase gene that sequesters arginine, a substrate for the microbicidal radical nitric oxide production (Angleró-Rodríguez et al., 2016). In a similar fashion, *Talaromyces* sp. isolated from field-collected *A. aegypti* facilitates Dengue virus infection by down-regulating digestive enzyme genes and trypsin activity (Angleró-Rodríguez et al., 2017). The introduction of *Serratia marcescens* in antibiotic-treated *A. aegypti* facilitates dengue virus dissemination and transmission through secretion of enhancin, which digests mucins of the mosquito's mucus layer (Wu et al., 2019).

The contribution of microbiota for the host's disease tolerance response is still poorly explored and future work is needed to elucidate its influence in insect immune modulation, vectorial competence and pathogen transmission.

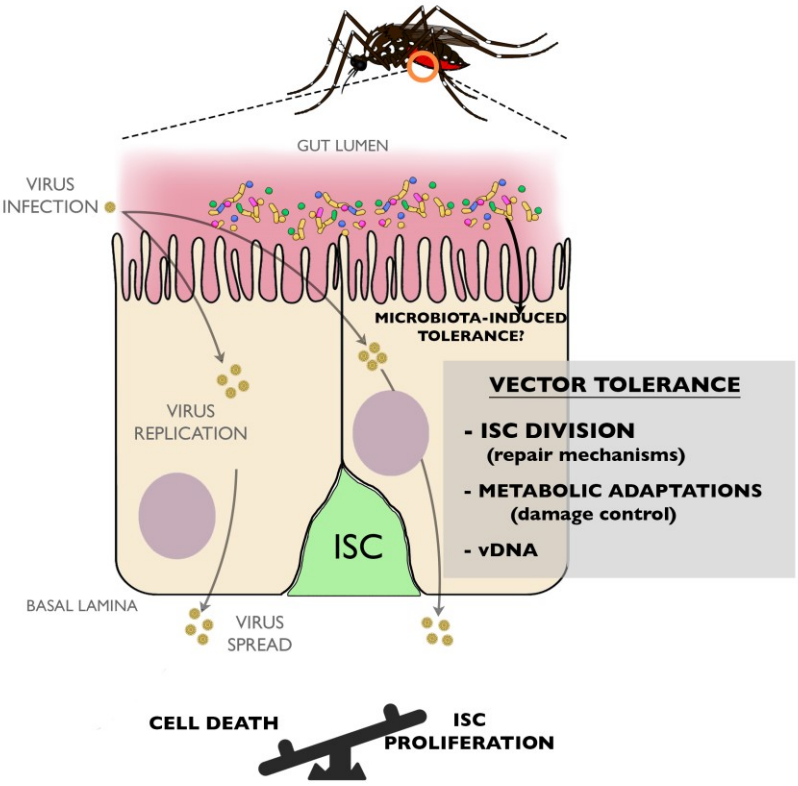

Figure 2: Possible tolerance mechanism operating in mosquito midgut during the first days following an infectious blood meal. Mechanisms driving mosquito disease tolerance to arbovirus infection may involve pathways that prevent molecular damage (damage control) and pathways that lead to organelle, cell and tissue repair once damage has occurred. It is possible that these pathways are also active in other tissues, such as brain, flight muscle, fat body, salivary glands and ovaries. Virus infection and replication in midgut epithelium will likely drive an adaptive tolerance response involving a balance between cell death and intestinal stem cell (ISC) division in order to keep gut integrity and homeostasis. At the same time, cellular energy reserves acting as stress sensors promote metabolic adaptations and virus-derived DNA (vDNA) is produced and promotes disease tolerance during infection. Several other mechanisms such as microbiota-induced tolerance are possible but, so far, still lack empirical evidence.

Box 3 – Outstanding questions in disease tolerance of arbovirus vectors

- How much do vectors vary in tolerance phenotypes within natural mosquito populations?
- How do mosquitos tolerate different viral pathogens?
- How do cellular renewal and vDNA contribute to vector disease tolerance?
- Are there fitness costs to the mosquito in tolerating viral infection (reduced fecundity/lifespan)?
- Is there a role for mosquito gut microbiota in the ability to tolerate arbovirus infections?

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References:

Allen, R.C., Popat, R., Diggle, S.P., Brown, S.P., 2014. Targeting virulence: can we make evolution-proof drugs? Nat Rev Microbiol 12, 300-308.

383 Anglero-Rodriguez, Y.I., Blumberg, B.J., Dong, Y., Sandiford, S.L., Pike, A., Clayton,
384 A.M., Dimopoulos, G., 2016. A natural Anopheles-associated Penicillium
385 chrysogenum enhances mosquito susceptibility to Plasmodium infection. Sci Rep 6,
386 34084.
387
388 Anglero-Rodriguez, Y.I., Talyuli, O.A., Blumberg, B.J., Kang, S., Demby, C., Shields, A.,
389 Carlson, J., Jupatanakul, N., Dimopoulos, G., 2017. An Aedes aegypti-associated
390 fungus increases susceptibility to dengue virus by modulating gut trypsin activity.
391 Elife 6.
392
393 Apte-Deshpande, A., Paingankar, M., Gokhale, M.D., Deobagkar, D.N., 2012. Serratia
394 odorifera a midgut inhabitant of Aedes aegypti mosquito enhances its susceptibility
395 to dengue-2 virus. PLoS One 7, e40401.
396
397 Arensburger, P., Hice, R.H., Wright, J.A., Craig, N.L., Atkinson, P.W., 2011. The
398 mosquito Aedes aegypti has a large genome size and high transposable element load
399 but contains a low proportion of transposon-specific piRNAs. BMC Genomics 12,
400 606.
401
402 Ayres, J.S., 2016. Cooperative Microbial Tolerance Behaviors in Host-Microbiota
403 Mutualism. Cell 165, 1323-1331.
404
405 Ayres, J.S., Schneider, D.S., 2008. A signaling protease required for melanization in
406 Drosophila affects resistance and tolerance of infections. PLoS Biol 6, 2764-2773.
407
408 Ayres, J.S., Schneider, D.S., 2012. Tolerance of infections. Annu Rev Immunol 30, 271-
409 294.
410
411 Bahia, A.C., Dong, Y., Blumberg, B.J., Mlambo, G., Tripathi, A., BenMarzouk-Hidalgo,
412 O.J., Chandra, R., Dimopoulos, G., 2014. Exploring Anopheles gut bacteria for
413 Plasmodium blocking activity. Environ Microbiol 16, 2980-2994.

Barletta, A.B., Nascimento-Silva, M.C., Talyuli, O.A., Oliveira, J.H., Pereira, L.O., Oliveira, P.L., Sorgine, M.H., 2017. Microbiota activates IMD pathway and limits Sindbis infection in Aedes aegypti. Parasit Vectors 10, 103.

Baucom, R., de Roode, J.C., 2011. Ecological immunology and tolerance in plants and animals. Functional Ecology 25, 18-28.

Bhatt, S., Gething, P.W., Brady, O.J., Messina, J.P., Farlow, A.W., Moyes, C.L., Drake, J.M., Brownstein, J.S., Hoen, A.G., Sankoh, O., Myers, M.F., George, D.B., Jaenisch, T., Wint, G.R., Simmons, C.P., Scott, T.W., Farrar, J.J., Hay, S.I., 2013. The global distribution and burden of dengue. Nature 496, 504-507.

Brandt, S.M., Dionne, M.S., Khush, R.S., Pham, L.N., Vigdal, T.J., Schneider, D.S., 2004. Secreted Bacterial Effectors and Host-Produced Eiger/TNF Drive Death in aSalmonella-Infected Fruit Fly. PLoS Biol 2, e418.

Buchon, N., Broderick, N.A., Chakrabarti, S., Lemaitre, B., 2009. Invasive and indigenous microbiota impact intestinal stem cell activity through multiple pathways in Drosophila. Genes Dev 23, 2333-2344.

Buchman, T., 2002. The community of the self. Nature 420, 246-251.

Chovatiya, R., Medzhitov, R. Stress, inflammation, and defense of homeostasis. Mol Cel 54, 281-288.

Cirimotich, C.M., Dong, Y., Clayton, A.M., Sandiford, S.L., Souza-Neto, J.A., Mulenga, M., Dimopoulos, G., 2011. Natural microbe-mediated refractoriness to Plasmodium infection in Anopheles gambiae. Science 332, 855-858.

444 Cirimotich, C.M., Scott, J.C., Phillips, A.T., Geiss, B.J., Olson, K.E., 2009. Suppression of
445 RNA interference increases alphavirus replication and virus-associated mortality in
446 Aedes aegypti mosquitoes. BMC Microbiol 9, 49.
447
448 Clayton, A.M., Cirimotich, C.M., Dong, Y., Dimopoulos, G., 2013. Caudal is a negative
449 regulator of the Anopheles IMD pathway that controls resistance to Plasmodium
450 falciparum infection. Dev Comp Immunol 39, 323-332.
451
452 Crochu, S., Cook, S., Attoui, H., Charrel, R.N., De Chesse, R., Belhouchet, M., Lemasson,
453 J.J., de Micco, P., de Lamballerie, X., 2004. Sequences of flavivirus-related RNA
454 viruses persist in DNA form integrated in the genome of Aedes spp. mosquitoes. J
455 Gen Virol 85, 1971-1980.
456
457 da Silveira, I.D., Petersen, M.T., Sylvestre, G., Garcia, G.A., David, M.R., Pavan, M.G.,
458 Maciel-de-Freitas, R., 2018. Zika Virus Infection Produces a Reduction on Aedes
459 aegypti Lifespan but No Effects on Mosquito Fecundity and Oviposition Success.
460 Front Microbiol 9, 3011.
461
462 Dharmarajan, G., Walker, K.D., Lehmann, T., 2018. Variation in tolerance to parasites
463 in natural Asian tiger mosquito populations and its effect on vectorial capacity.
464 bioRxiv.
465 Dong, Y., Manfredini, F., Dimopoulos, G., 2009. Implication of the mosquito midgut
466 microbiota in the defense against malaria parasites. PLoS Pathog 5, e1000423.
467
468 Eng, M.W., van Zuylen, M.N., Severson, D.W., 2016. Apoptosis-related genes control
469 autophagy and influence DENV-2 infection in the mosquito vector, Aedes aegypti.
470 Insect Biochem Mol Biol 76, 70-83.
471
472 Ganeshan, K., Nikkanen, J., Man, K., Leong, Y.A., Sogawa, Y., Maschek, J.A., Van Ry, T.,
473 Chagwedera, D.N., Cox, J.E., Chawla, A., 2019. Energetic Trade-Offs and
474 Hypometabolic States Promote Disease Tolerance. Cell 177, 399-413 e312.

Goic, B., Stapleford, K.A., Frangeul, L., Doucet, A.J., Gausson, V., Blanc, H., Schemmel-Jofre, N., Cristofari, G., Lambrechts, L., Vignuzzi, M., Saleh, M.C., 2016. Virus-derived DNA drives mosquito vector tolerance to arboviral infection. Nat Commun 7, 12410.

Grubaugh, N.D., Fauver, J.R., Ruckert, C., Weger-Lucarelli, J., Garcia-Luna, S., Murrieta, R.A., Gendernalik, A., Smith, D.R., Brackney, D.E., Ebel, G.D., 2017. Mosquitoes Transmit Unique West Nile Virus Populations during Each Feeding Episode. Cell Rep 19, 709-718.

Gupta, V., Vale, P.F., 2017. Nonlinear disease tolerance curves reveal distinct components of host responses to viral infection. R Soc Open Sci 4, 170342.

Han, C., Song, Y., Xiao, H., Wang, D., Franc, N.C., Jan, L.Y., Jan, Y.N., 2014. Epidermal cells are the primary phagocytes in the fragmentation and clearance of degenerating dendrites in Drosophila. Neuron 81, 544-560.

Henschen, A.E., Adelman, J.S., 2019. What Does Tolerance Mean for Animal Disease Dynamics When Pathology Enhances Transmission? Integr Comp Biol.

Hoffmann, J.A., Kafatos, F.C., Janeway, C.A., Ezekowitz, R.A., 1999. Phylogenetic perspectives in innate immunity. Science 284, 1313-1318.

Hongoh, Y., Sharma, V.K., Prakash, T., Noda, S., Toh, H., Taylor, T.D., Kudo, T., Sakaki, Y., Toyoda, A., Hattori, M., Ohkuma, M., 2008. Genome of an endosymbiont coupling N2 fixation to cellulolysis within protist cells in termite gut. Science 322, 1108-1109.

Howick, V.M., Lazzaro, B.P., 2017. The genetic architecture of defence as resistance to and tolerance of bacterial infection in Drosophila melanogaster. Mol Ecol 26, 1533-1546.

506 Hoze, N., Bonhoeffer, S., Regoes, R., 2018. Assessing the public health impact of
507 tolerance-based therapies with mathematical models. PLoS Comput Biol 14,
508 e1006119.
509
510 Jamieson, A.M., Pasman, L., Yu, S., Gamradt, P., Homer, R.J., Decker, T., Medzhitov, R.,
511 2013. Role of tissue protection in lethal respiratory viral-bacterial coinfection.
512 Science 340, 1230-1234.
513
514 Janeh, M., Osman, D., Kambris, Z., 2017. Damage-Induced Cell Regeneration in the
515 Midgut of Aedes albopictus Mosquitoes. Sci Rep 7, 44594.
516
517 Kikuchi, Y., Hayatsu, M., Hosokawa, T., Nagayama, A., Tago, K., Fukatsu, T., 2012.
518 Symbiont-mediated insecticide resistance. Proc Natl Acad Sci U S A 109, 8618-8622.
519
520 Lambrechts, L., Scott, T.W., 2009. Mode of transmission and the evolution of
521 arbovirus virulence in mosquito vectors. Proc Biol Sci 276, 1369-1378.
522
523 Lambrechts, L., Saleh, M.C. Manipulating mosquito tolerance for arbovirus control.
524 Cell Host Microb 26, 309-313.
525
526 Lefevre, T., Williams, A.J., de Roode, J.C., 2011. Genetic variation in resistance, but not
527 tolerance, to a protozoan parasite in the monarch butterfly. Proc Biol Sci 278, 751-
528 759.
529
530 Lissner, M.M., Schneider, D.S., 2018. The physiological basis of disease tolerance in
531 insects. Curr Opin Insect Sci 29, 133-136.
532
533 Lissner, M.M., Schneider, D.S., 2018. The physiological basis of disease tolerance in
534 insects. Curr Opin Insect Sci 29, 133-136.
535

536 Louie, A., Song, K.H., Hotson, A., Thomas Tate, A., Schneider, D.S., 2016. How Many
537 Parameters Does It Take to Describe Disease Tolerance? PLoS Biol 14, e1002435.
538
539 Mace, K.A., Pearson, J.C., McGinnis, W., 2005. An epidermal barrier wound repair
540 pathway in Drosophila is mediated by grainy head. Science 308, 381-385.
541
542 Martin, E., Moutailler, S., Madec, Y., Failloux, A.B., 2010. Differential responses of the
543 mosquito Aedes albopictus from the Indian Ocean region to two chikungunya
544 isolates. BMC Ecol 10, 8.
545
546 Martins, R., Carlos, A.R., Braza, F., Thompson, J.A., Bastos-Amador, P., Ramos, S.,
547 Soares, M.P., 2019. Disease Tolerance as an Inherent Component of Immunity. Annu
548 Rev Immunol 37, 405-437.
549
550 Merkling, S.H., Bronkhorst, A.W., Kramer, J.M., Overheul, G.J., Schenck, A., Van Rij,
551 R.P., 2015. The epigenetic regulator G9a mediates tolerance to RNA virus infection
552 in Drosophila. PLoS Pathog 11, e1004692.
553
554 Miesen, P., Girardi, E., van Rij, R.P., 2015. Distinct sets of PIWI proteins produce
555 arbovirus and transposon-derived piRNAs in Aedes aegypti mosquito cells. Nucleic
556 Acids Res 43, 6545-6556.
557
558 Miesen, P., Joosten, J., van Rij, R.P., 2016. PIWIs Go Viral: Arbovirus-Derived piRNAs
559 in Vector Mosquitoes. PLoS Pathog 12, e1006017.
560
561 Miller, M.R., White, A., Boots, M., 2005. The evolution of host resistance: tolerance
562 and control as distinct strategies. J Theor Biol 236, 198-207.
563
564 Morazzani, E.M., Wiley, M.R., Murreddu, M.G., Adelman, Z.N., Myles, K.M., 2012.
565 Production of virus-derived ping-pong-dependent piRNA-like small RNAs in the
566 mosquito soma. PLoS Pathog 8, e1002470.

Moreno-Garcia, M., Recio-Totoro, B., Claudio-Piedras, F., Lanz-Mendoza, H., 2014. Injury and immune response: applying the danger theory to mosquitoes. Front Plant Sci 5, 451.

Myles, K.M., Wiley, M.R., Morazzani, E.M., Adelman, Z.N., 2008. Alphavirus-derived small RNAs modulate pathogenesis in disease vector mosquitoes. Proc Natl Acad Sci U S A 105, 19938-19943.

Nag, D.K., Brecher, M., Kramer, L.D., 2016. DNA forms of arboviral RNA genomes are generated following infection in mosquito cell cultures. Virology 498, 164-171.

Nag, D.K., Kramer, L.D., 2017. Patchy DNA forms of the Zika virus RNA genome are generated following infection in mosquito cell cultures and in mosquitoes. J Gen Virol 98, 2731-2737.

Nikoh, N., Hosokawa, T., Oshima, K., Hattori, M., Fukatsu, T., 2011. Reductive evolution of bacterial genome in insect gut environment. Genome Biol Evol 3, 702-714.

O'Neill, K., Olson, B.J., Huang, N., Unis, D., Clem, R.J., 2015. Rapid selection against arbovirus-induced apoptosis during infection of a mosquito vector. Proc Natl Acad Sci U S A 112, E1152-1161.

Ocampo, C.B., Caicedo, P.A., Jaramillo, G., Ursic Bedoya, R., Baron, O., Serrato, I.M., Cooper, D.M., Lowenberger, C., 2013. Differential expression of apoptosis related genes in selected strains of Aedes aegypti with different susceptibilities to dengue virus. PLoS One 8, e61187.

Olmo, R.P., Ferreira, A.G.A., Izidoro-Toledo, T.C., Aguiar, E., de Faria, I.J.S., de Souza, K.P.R., Osorio, K.P., Kuhn, L., Hammann, P., de Andrade, E.G., Todjro, Y.M., Rocha,

598 M.N., Leite, T., Amadou, S.C.G., Armache, J.N., Paro, S., de Oliveira, C.D., Carvalho, F.D.,
599 Moreira, L.A., Marois, E., Imler, J.L., Marques, J.T., 2018. Control of dengue virus in
600 the midgut of Aedes aegypti by ectopic expression of the dsRNA-binding protein
601 Loqs2. Nat Microbiol 3, 1385-1393.
602
603 Palatini, U., Miesen, P., Carballar-Lejarazu, R., Ometto, L., Rizzo, E., Tu, Z., van Rij, R.P.,
604 Bonizzoni, M., 2017. Comparative genomics shows that viral integrations are
605 abundant and express piRNAs in the arboviral vectors Aedes aegypti and Aedes
606 albopictus. BMC Genomics 18, 512.
607
608 Petersen, M.T., Silveira, I.D.D., Tatila-Ferreira, A., David, M.R., Chouin-Carneiro, T.,
609 Van den Wouwer, L., Maes, L., Maciel-de-Freitas, R., 2018. The impact of the age of
610 first blood meal and Zika virus infection on Aedes aegypti egg production and
611 longevity. PLoS One 13, e0200766.
612
613 Ping, L., Buchler, R., Mithofer, A., Svatos, A., Spiteller, D., Dettner, K., Gmeiner, S., Piel,
614 J., Schlott, B., Boland, W., 2007. A novel Dps-type protein from insect gut bacteria
615 catalyses hydrolysis and synthesis of N-acyl amino acids. Environ Microbiol 9, 1572-
616 1583.
617
618 Poirier, E.Z., Goic, B., Tome-Poderti, L., Frangeul, L., Boussier, J., Gausson, V., Blanc,
619 H., Vallet, T., Loyd, H., Levi, L.I., Lanciano, S., Baron, C., Merkling, S.H., Lambrechts, L.,
620 Mirouze, M., Carpenter, S., Vignuzzi, M., Saleh, M.C., 2018. Dicer-2-Dependent
621 Generation of Viral DNA from Defective Genomes of RNA Viruses Modulates
622 Antiviral Immunity in Insects. Cell Host Microbe 23, 353-365 e358.
623
624 Raberg, L., Graham, A.L., Read, A.F., 2009. Decomposing health: tolerance and
625 resistance to parasites in animals. Philos Trans R Soc Lond B Biol Sci 364, 37-49.
626
627 Raberg, L., Sim, D., Read, A.F., 2007. Disentangling genetic variation for resistance
628 and tolerance to infectious diseases in animals. Science 318, 812-814.

Ramirez, J.L., Short, S.M., Bahia, A.C., Saraiva, R.G., Dong, Y., Kang, S., Tripathi, A., Mlambo, G., Dimopoulos, G., 2014. Chromobacterium Csp_P reduces malaria and dengue infection in vector mosquitoes and has entomopathogenic and in vitro anti-pathogen activities. PLoS Pathog 10, e1004398.

Rangan, K.J., Pedicord, V.A., Wang, Y.C., Kim, B., Lu, Y., Shaham, S., Mucida, D., Hang, H.C., 2016. A secreted bacterial peptidoglycan hydrolase enhances tolerance to enteric pathogens. Science 353, 1434-1437.

Rasko, D.A., Sperandio, V., 2010. Anti-virulence strategies to combat bacteria-mediated disease. Nat Rev Drug Discov 9, 117-128.

Read, A.F., Baigent, S.J., Powers, C., Kgosana, L.B., Blackwell, L., Smith, L.P., Kennedy, D.A., Walkden-Brown, S.W., Nair, V.K., 2015. Imperfect Vaccination Can Enhance the Transmission of Highly Virulent Pathogens. PLoS Biol 13, e1002198.

Regoes, R.R., McLaren, P.J., Battegay, M., Bernasconi, E., Calmy, A., Gunthard, H.F., Hoffmann, M., Rauch, A., Telenti, A., Fellay, J., Swiss, H.I.V.C.S., 2014. Disentangling human tolerance and resistance against HIV. PLoS Biol 12, e1001951.

Reiskind, M.H., Westbrook, C.J., Lounibos, L.P., 2010. Exposure to chikungunya virus and adult longevity in Aedes aegypti (L.) and Aedes albopictus (Skuse). J Vector Ecol 35, 61-68.

Ripert, G., Racedo, S.M., Elie, A.M., Jacquot, C., Bressollier, P., Urdaci, M.C., 2016. Secreted Compounds of the Probiotic Bacillus clausii Strain O/C Inhibit the Cytotoxic Effects Induced by Clostridium difficile and Bacillus cereus Toxins. Antimicrob Agents Chemother 60, 3445-3454.

658 Rodgers, F.H., Gendrin, M., Wyer, C.A.S., Christophides, G.K., 2017. Microbiota-
659 induced peritrophic matrix regulates midgut homeostasis and prevents systemic
660 infection of malaria vector mosquitoes. PLoS Pathog 13, e1006391.
661
662 Sahoo, M., Del Barrio, L., Miller, M.A., Re, F., 2014. Neutrophil elastase causes tissue
663 damage that decreases host tolerance to lung infection with burkholderia species.
664 PLoS Pathog 10, e1004327.
665
666 Salazar, M.I., Richardson, J.H., Sanchez-Vargas, I., Olson, K.E., Beaty, B.J., 2007.
667 Dengue virus type 2: replication and tropisms in orally infected Aedes aegypti
668 mosquitoes. BMC Microbiol 7, 9.
669
670 Sanchez-Vargas, I., Scott, J.C., Poole-Smith, B.K., Franz, A.W., Barbosa-Solomieu, V.,
671 Wilusz, J., Olson, K.E., Blair, C.D., 2009. Dengue virus type 2 infections of Aedes
672 aegypti are modulated by the mosquito's RNA interference pathway. PLoS Pathog 5,
673 e1000299.
674
675 Saraiva, R.G., Fang, J., Kang, S., Anglero-Rodriguez, Y.I., Dong, Y., Dimopoulos, G.,
676 2018. Aminopeptidase secreted by Chromobacterium sp. Panama inhibits dengue
677 virus infection by degrading the E protein. PLoS Negl Trop Dis 12, e0006443.
678
679 Saraiva, R.G., Huitt-Roehl, C.R., Tripathi, A., Cheng, Y.Q., Bosch, J., Townsend, C.A.,
680 Dimopoulos, G., 2018. Chromobacterium spp. mediate their anti-Plasmodium
681 activity through secretion of the histone deacetylase inhibitor romidepsin. Sci Rep 8,
682 6176.
683
684 Saraiva, R.G., Kang, S., Simoes, M.L., Anglero-Rodriguez, Y.I., Dimopoulos, G., 2016.
685 Mosquito gut antiparasitic and antiviral immunity. Dev Comp Immunol 64, 53-64.
686

687 Schneider, D.S., Ayres, J.S., 2008. Two ways to survive infection: what resistance and
688 tolerance can teach us about treating infectious diseases. Nat Rev Immunol 8, 889-
689 895.
690
691 Schnettler, E., Donald, C.L., Human, S., Watson, M., Siu, R.W., McFarlane, M.,
692 Fazakerley, J.K., Kohl, A., Fragkoudis, R., 2013. Knockdown of piRNA pathway
693 proteins results in enhanced Semliki Forest virus production in mosquito cells. J Gen
694 Virol 94, 1680-1689.
695
696 Shaw, D.K., Tate, A.T., Schneider, D.S., Levashina, E.A., Kagan, J.C., Pal, U., Fikrig, E.,
697 Pedra, J.H.F., 2018. Vector Immunity and Evolutionary Ecology: The Harmonious
698 Dissonance. Trends Immunol 39, 862-873.
699
700 Shin, S.C., Kim, S.H., You, H., Kim, B., Kim, A.C., Lee, K.A., Yoon, J.H., Ryu, J.H., Lee, W.J.,
701 2011. Drosophila microbiome modulates host developmental and metabolic
702 homeostasis via insulin signaling. Science 334, 670-674.
703
704 Sirisena, P., Kumar, A., Sunil, S., 2018. Evaluation of Aedes aegypti (Diptera:
705 Culicidae) Life Table Attributes Upon Chikungunya Virus Replication Reveals Impact
706 on Egg-Laying Pathways. J Med Entomol 55, 1580-1587.
707
708 Soares, M.P., Gozzelino, R., Weis, S., 2014. Tissue damage control in disease
709 tolerance. Trends Immunol 35, 483-494.
710
711 Soares, M.P., Teixeira, L., Moita, L.F., 2017. Disease tolerance and immunity in host
712 protection against infection. Nat Rev Immunol 17, 83-96.
713
714 Soares, M.P., Teixeira, L., Moita, L.F., 2017. Disease tolerance and immunity in host
715 protection against infection. Nat Rev Immunol 17, 83-96.
716

717 Souza-Neto, J.A., Sim, S., Dimopoulos, G., 2009. An evolutionary conserved function
718 of the JAK-STAT pathway in anti-dengue defense. Proc Natl Acad Sci U S A 106,
719 17841-17846.
720
721 Sterkel, M., Oliveira, J.H., Bottino-Rojas, V., Paiva-Silva, G.O., Oliveira, P.l., 2017. The
722 dose makes the poison: Nutritional overload determines the life traits of blood-
723 feeding arthropods. Trends Parasitol 33, 633-644.
724
725 Sternberg, E.D., Lefevre, T., Li, J., de Castillejo, C.L., Li, H., Hunter, M.D., de Roode, J.C.,
726 2012. Food plant derived disease tolerance and resistance in a natural butterfly-
727 plant-parasite interactions. Evolution 66, 3367-3376.
728
729 Sternberg, E.D., Li, H., Wang, R., Gowler, C., de Roode, J.C., 2013. Patterns of host-
730 parasite adaptation in three populations of monarch butterflies infected with a
731 naturally occurring protozoan disease: virulence, resistance, and tolerance. Am Nat
732 182, E235-248.
733
734 Suzuki, Y., Frangeul, L., Dickson, L.B., Blanc, H., Verdier, Y., Vinh, J., Lambrechts, L.,
735 Saleh, M.C., 2017. Uncovering the Repertoire of Endogenous Flaviviral Elements in
736 Aedes Mosquito Genomes. J Virol 91.
737
738 Taracena, M.L., Bottino-Rojas, V., Talyuli, O.A.C., Walter-Nuno, A.B., Oliveira, J.H.M.,
739 Anglero-Rodriguez, Y.I., Wells, M.B., Dimopoulos, G., Oliveira, P.L., Paiva-Silva, G.O.,
740 2018. Regulation of midgut cell proliferation impacts Aedes aegypti susceptibility to
741 dengue virus. PLoS Negl Trop Dis 12, e0006498.
742
743 Teixeira, L., Ferreira, A., Ashburner, M., 2008. The bacterial symbiont Wolbachia
744 induces resistance to RNA viral infections in Drosophila melanogaster. PLoS Biol 6,
745 e2.
746 Tesla, B., Demakovsky, L.R., Packiam, H.S., Mordecai, E.A., Rodriguez, A.D., Bonds,
747 M.H., Brindley, M.A., Murdock, C.C., 2018. Estimating the effects of variation in

viremia on mosquito susceptibility, infectiousness, and R0 of Zika in Aedes aegypti. PLoS Negl Trop Dis 12, e0006733.

Thaker, S.K., Chapa, T., Garcia, G., Jr., Gong, D., Schmid, E.W., Arumugaswami, V., Sun, R., Christofk, H.R., 2019. Differential Metabolic Reprogramming by Zika Virus Promotes Cell Death in Human versus Mosquito Cells. Cell Metab 29, 1206-1216 e1204.

Troha, K., Im, J.H., Revah, J., Lazzaro, B.P., Buchon, N., 2018. Comparative transcriptomics reveals CrebA as a novel regulator of infection tolerance in D. melanogaster. PLoS Pathog 14, e1006847.

Vale, P.F., Choisy, M., Little, T.J., 2013. Host nutrition alters the variance in parasite transmission potential. Biol Lett 9, 20121145.

Vale, P.F., Fenton, A., Brown, S.P., 2014. Limiting damage during infection: lessons from infection tolerance for novel therapeutics. PLoS Biol 12, e1001769.

Vale, P.F., Little, T.J., 2012. Fecundity compensation and tolerance to a sterilizing pathogen in Daphnia. J Evol Biol 25, 1888-1896.

Vale, P.F., Wilson, A.J., Best, A., Boots, M., Little, T.J., 2011. Epidemiological, evolutionary, and coevolutionary implications of context-dependent parasitism. Am Nat 177, 510-521.

Wang, H., Gort, T., Boyle, D.L., Clem, R.J., 2012. Effects of manipulating apoptosis on Sindbis virus infection of Aedes aegypti mosquitoes. J Virol 86, 6546-6554.

Warnecke, F., Luginbuhl, P., Ivanova, N., Ghassemian, M., Richardson, T.H., Stege, J.T., Cayouette, M., McHardy, A.C., Djordjevic, G., Aboushadi, N., Sorek, R., Tringe, S.G., Podar, M., Martin, H.G., Kunin, V., Dalevi, D., Madejska, J., Kirton, E., Platt, D., Szeto, E.,

779 Salamov, A., Barry, K., Mikhailova, N., Kyrpides, N.C., Matson, E.G., Ottesen, E.A.,
780 Zhang, X., Hernandez, M., Murillo, C., Acosta, L.G., Rigoutsos, I., Tamayo, G., Green,
781 B.D., Chang, C., Rubin, E.M., Mathur, E.J., Robertson, D.E., Hugenholtz, P., Leadbetter,
782 J.R., 2007. Metagenomic and functional analysis of hindgut microbiota of a wood-
783 feeding higher termite. Nature 450, 560-565.
784
785 Whitfield, Z.J., Dolan, P.T., Kunitomi, M., Tassetto, M., Seetin, M.G., Oh, S., Heiner, C.,
786 Paxinos, E., Andino, R., 2017. The Diversity, Structure, and Function of Heritable
787 Adaptive Immunity Sequences in the Aedes aegypti Genome. Curr Biol 27, 3511-
788 3519 e3517.
789
790 Wu, P., Sun, P., Nie, K., Zhu, Y., Shi, M., Xiao, C., Liu, H., Liu, Q., Zhao, T., Chen, X., Zhou,
791 H., Wang, P., Cheng, G., 2019. A Gut Commensal Bacterium Promotes Mosquito
792 Permissiveness to Arboviruses. Cell Host Microbe 25, 101-112 e105.
793
794 Xi, Z., Ramirez, J.L., Dimopoulos, G., 2008. The Aedes aegypti toll pathway controls
795 dengue virus infection. PLoS Pathog 4, e1000098.
796
797