

HOST RESPONSE

STING'ing Zika virus in neurons

Studies in *Drosophila* reveal that the insect homologue of the stimulator of interferon genes (STING) exerts antiviral activity against Zika virus infection in the fly brain through the induction of autophagy, providing key insights into the possible evolutionary function of STING in antiviral defence.

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Flaviviruses are arthropod-borne viruses that are transmitted most commonly by *Aedes* mosquito vectors. They represent a threat to human health worldwide and include viruses such as dengue, West Nile, yellow fever and Zika. The global impact of flaviviruses was appreciated more recently when a large worldwide Zika virus (ZIKV) outbreak was associated with severe congenital anomalies when the virus was vertically transmitted to developing fetuses following infection of pregnant women. In fetuses, ZIKV preferentially targets and damages neural stem cells and progenitor cells, leading to fetal brain abnormalities. In adults, ZIKV infections are associated with comparatively much milder outcomes, but complications associated with the central nervous system can occur in rare cases. The intracellular host pathways that control ZIKV infections in fetal cells remain largely undefined. Moreover, given that ZIKV is an arthropod-borne virus and its life cycle includes stages in an insect and human host, whether these pathways are shared between disparate hosts remains unclear. In an article recently published in *Cell Host & Microbe*, Liu et al. report on the use of a *Drosophila melanogaster* model to interrogate the pathways present in neurons that control ZIKV infection¹. The authors show that *Drosophila* exploits the highly evolutionarily conserved molecule stimulator of interferon genes (STING) to suppress ZIKV infection specifically in the fly brain. This study therefore defines the function of *Drosophila* STING in antiviral signalling and points to a role for STING-mediated signalling in the control of ZIKV infection of neurons.

Using *Drosophila* as a model organism, Liu et al. show that ZIKV preferentially infects the fly brain, mimicking the cellular tropism of this virus in the developing human brain. This infection induces an inflammatory signalling cascade mediated by nuclear factor κ B (NF- κ B), but not by other *Drosophila*-associated innate pathways such as RNA interference (RNAi). Importantly, although

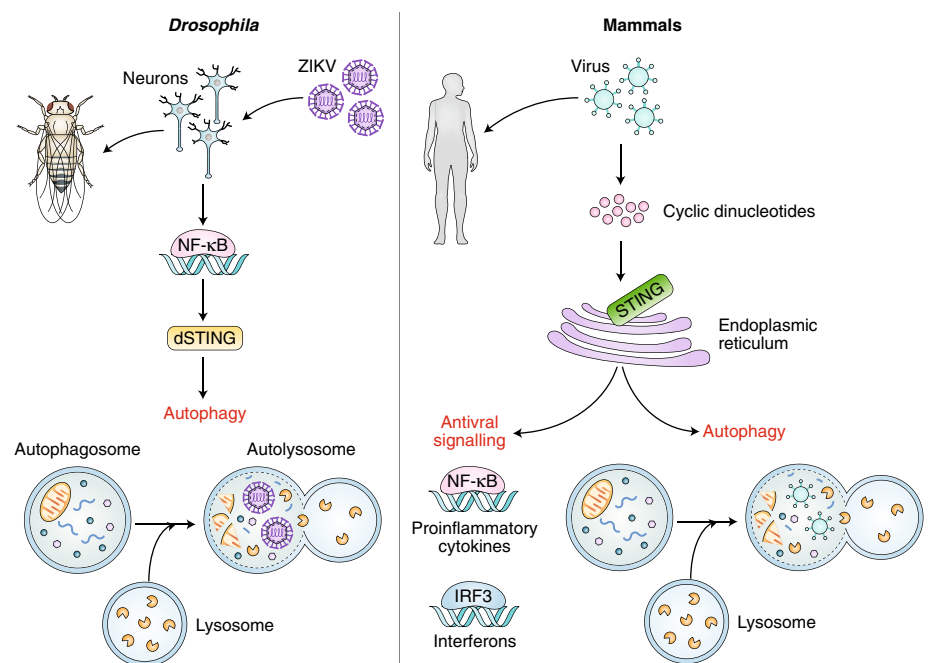


Fig. 1 | Illustration of the different roles of STING-mediated antiviral defence in *Drosophila* and mammals. Liu et al. show that the expression of dSTING is induced by NF- κ B signalling in response to ZIKV infection in the fly brain (left panel). Elevated STING expression leads to autophagy, an evolutionarily conserved degradative pathway in which autophagosomes fuse with lysosomes to form the autolysosome, which sequesters viral particles and destroys them. In mammalian cells (right panel) endoplasmic-reticulum-localized STING becomes activated in response to viral infections via the generation of cyclic dinucleotides, which leads to the induction of proinflammatory cytokines by NF- κ B and antiviral IFNs through interferon regulatory factors (IRFs), as well as autophagy. *Drosophila* (left panel) does not express IRFs and thus lacks IFN signalling, indicating that autophagy may be an evolutionarily conserved downstream pathway of STING to restrict the replication of intracellular pathogens.

the induction of interferons (IFNs) is the primary defensive pathway induced in mammalian cells to combat viral infections, *Drosophila* lacks this pathway and therefore relies on other signalling pathways to restrict viral infections. To define the downstream effectors of NF- κ B signalling in infected *Drosophila*, the authors performed transcriptional profiling in flies infected with *Drosophila* C virus (DCV), a picornavirus that naturally infects *Drosophila*. Not unexpectedly, the authors

found that many of the induced genes were canonical effectors associated with NF- κ B signalling. However, when analysing their data, the authors also found that infection induced the expression of the *Drosophila* homologue of STING, named dSTING. STING is a highly evolutionarily conserved molecule that responds to both exogenous and endogenous ligands (cyclic dinucleotides) to trigger the innate immune system^{2,3}. Although flies were known to encode an orthologue of

STING, its role in innate immune sensing and pathogen clearance was unknown as invertebrates lack functional IFN signalling. Consequently, dSTING — like other STING orthologues in invertebrates — lacks the domain involved in IFN signalling, the CTT domain, but does contain several other domains involved in other STING-induced downstream pathways². Utilizing the power of *Drosophila* genetics, the authors show that deletion of dSTING in the whole fly, or in neuronal cells (neurons and glia), leads to significant elevation of ZIKV replication only in the fly brain, but not in other organs. These data, for the first time, show that dSTING plays a central role in antiviral defence in *Drosophila*, particularly in the brain.

To identify the downstream signalling pathways involved in viral restriction, the authors explore the possibility that dSTING may control autophagy, as does its mammalian counterpart^{4,5}. Autophagy is one of the most evolutionarily conserved pathways utilized by cells to clear damaged organelles to maintain cellular homeostasis. Given that autophagic vesicles deliver their contents to degradative lysosomes, autophagy has recently emerged as a

common pathway to restrict the replication of intracellular pathogens in different cell types and species. However, the cellular factors across vertebrates and invertebrates that control this pathway are poorly characterized and the role of STING in regulating autophagy in invertebrates remains to be demonstrated. Liu et al. show that dSTING is required for the induction of autophagy in response to ZIKV infection of *Drosophila* and that ablation of this pathway (utilizing genetic mutants of dSTING) leads to increased ZIKV replication specifically in the fly brain. These data point to a direct role for dSTING in the induction of antiviral autophagy in *Drosophila* and suggest that this pathway may be particularly important in terminally differentiated cells such as neurons. In a study published in parallel in *Cell Reports*, Martin et al. also point to a role for dSTING in the protection of *Drosophila* from bacterial infections (*Listeria monocytogenes*)⁶. The work by Liu et al. thus provides fundamental advances in our understanding of how STING exerts antiviral functions in invertebrates (Fig. 1). This study also suggests that STING-mediated autophagy may provide an evolutionarily conserved means to

protect differentiated neurons, which lack self-renewal, from more cytotoxic forms of antiviral defence. □

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Competing interests

The authors declare no competing interests.