Discovery in mosquitoes could lead to new strategy against dengue fever and other mosquito-borne vectors

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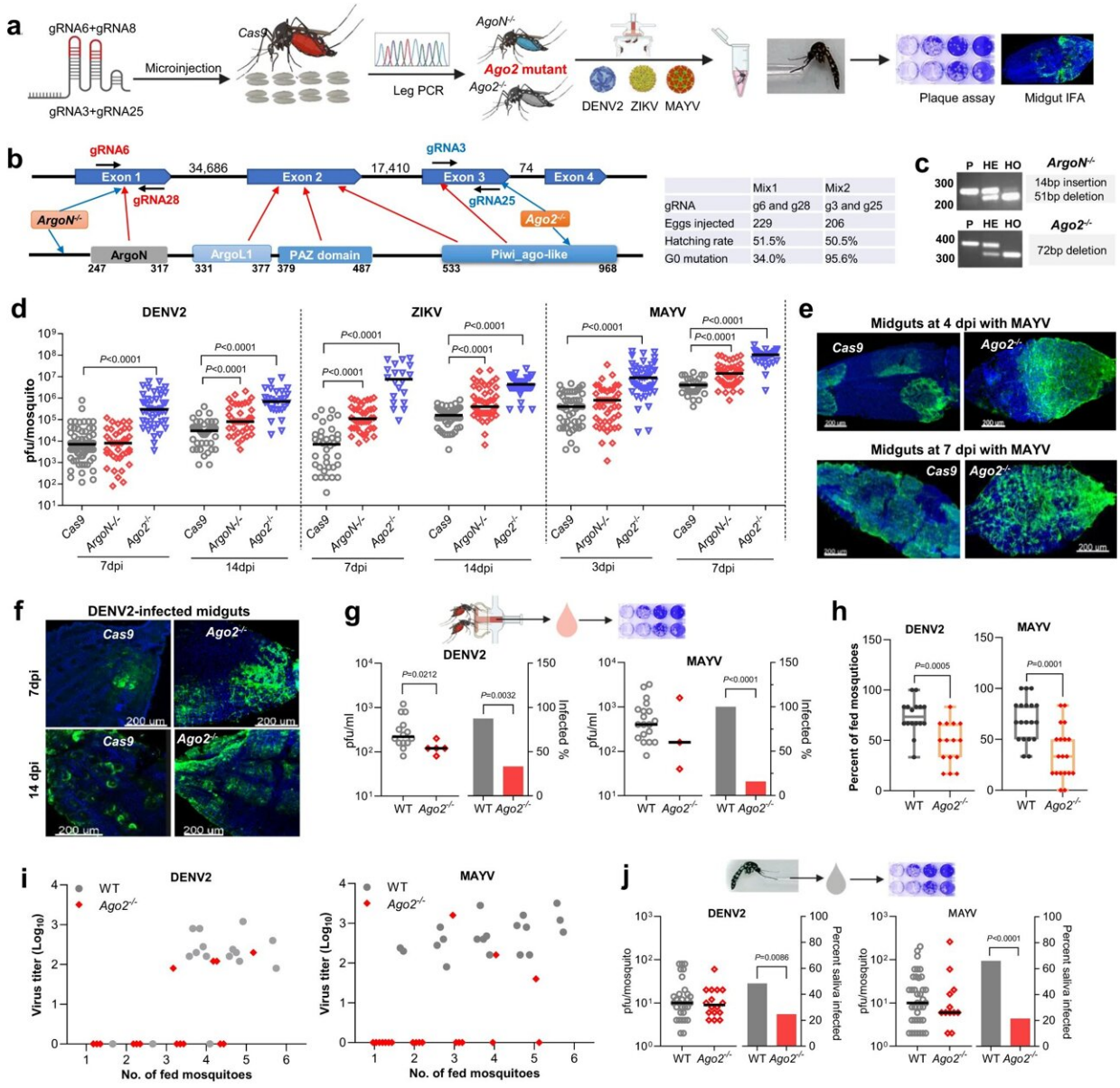

Generation of *Ago2* knockout *Ae. aegypti* lines and the effect of *Ago2* disruption on arbovirus infection and transmission. **a** flowchart of experiment design. **b** gene structure of *Ago2*, predicted functional domains, and guide RNA (gRNA) design for CRISPR/Cas9. The table shows data from generating *Ago2* knockout lines. **c** *Ago2* amplification in *Ago2* knockout lines. P, parental line *Cas9*; HE, heterozygous mutants; HO, homozygous mutants. **d** virus titer in *Ago2* knockout ($Ago2^{-/-}$ and $ArgoN^{-/-}$) and *Cas9* mosquitoes on various days post-infection (dpi) with DENV2, ZIKV, or MAYV. IFA detection of MAYV (**e**) and DENV2 (**f**) antigen in midguts of *Cas9* and $Ago2^{-/-}$ mosquitoes at different days post virus infection. MAYV and DENV2 were detected with the corresponding monoclonal antibody (green). Nuclei were stained with DAPI (blue). **g** virus titer and infection prevalence in the feeding solution collected from a feeder exposed to a group of females at 14 dpi with DENV2 or 5 dpi with MAYV. The Liverpool strain was used as a control (WT). For DENV2 infection, $n = 16$ for WT and $n = 15$ for $Ago2^{-/-}$; for MAYV infection, $n = 19$ for both WT and $Ago2^{-/-}$. **h** percentage of the fed mosquitoes in each group of females at 14 dpi with DENV2 or 5 dpi with MAYV. Data were presented as box and whiskers (Min to Max). **i** virus titer plotted against the number of the fed mosquitoes in each cup. **j** virus titer and infection prevalence of individual saliva samples collected from $Ago2^{-/-}$ and WT at 14 dpi with DENV2 or 5 dpi with MAYV. For DENV2 infection, $n = 62$ for WT and $n = 61$ for $Ago2^{-/-}$; for MAYV infection, $n = 56$ for both WT and $Ago2^{-/-}$. Each experiment comprised at least two biological replicates, and the data were pooled for generating the graphs. Virus titers were determined by plaque assay, and horizontal lines indicate the medians of the virus titer (**d**, **g** and **j**). *P* values were determined by an unpaired two-sided Mann-Whitney test for virus titer, an unpaired two-sided Fisher's exact test for infection prevalence, or an unpaired two-sided *t*-test for (**h**). Source data are provided as a Source Data file. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-41370-y

Researchers from the Johns Hopkins Malaria Research Institute at the Johns Hopkins Bloomberg School of Public Health have made an

important finding about Aedes aegypti mosquitoes—one that could one day lead to better methods for reducing the mosquito-to-human transmission of dengue, yellow fever, Zika, and other harmful and sometimes deadly viruses.

Ae. aegypti mosquitoes do not succumb to these viruses when infected and continue to move and feed normally. As such, the infected mosquitoes can pass their viral cargoes on to humans. The researchers discovered that an Ae. aegypti protein, Argonaute 2, has a key role—via several biological mechanisms—in keeping mosquitoes healthy and active despite these infections.

The discovery represents a significant advance in understanding mosquito biology. It also hints at a strategy that would aim to shut down Ae. aegypti mosquitoes' defenses whenever they become infected by certain viruses—killing the mosquitoes and thereby reducing the transmission of those viruses by Ae. aegypti to humans.

Instead of making mosquitoes more resistant to the viruses, the discovery opens a possible path for making mosquitoes more susceptible and less tolerant to virus infection, which would impair their ability to transmit disease.

The research was published online September 18 in *Nature Communications*.

"Researchers have long wondered why Ae. aegypti mosquitoes don't get sick when they are infected by these viruses—our findings effectively solve this mystery and suggest a potential new mosquito-based disease control strategy that merits further study," says study senior author George Dimopoulos, Ph.D., a professor in the Johns Hopkins Malaria Research Institute and in the Bloomberg School's Department of Molecular Microbiology and Immunology.

The study's lead author was Shengzhang Dong, Ph.D., a senior research associate in the Bloomberg School's Department of Molecular Microbiology and Immunology.

Ae. aegypti mosquitoes transmit "arthropod-borne" or "arbo-" viruses including dengue virus, yellow fever virus, Zika virus, chikungunya virus, and Mayaro virus. Each year these pathogens sicken millions of people around the world each year, killing tens of thousands. There are no antiviral therapies for any of these viruses.

Currently, a vaccine is available for yellow fever virus. One dengue vaccine is approved by the Food and Drug Administration for individuals between six and 16 who have had prior dengue infection. Disease control methods for Ae. aegyptiemphasize the use of insecticides, which have had limited success and have led to insecticide resistance.

Ae. aegypti mosquitoes are effective vectors of arborviruses because they can sustain significant infections with these viruses without suffering costs to their overall ability to reproduce—what biologists call "fitness." If the mosquitoes' fitness was impaired, they would likely have evolved strong defenses against these pathogens. Instead, they somehow ended up with a live-and-let-live balance that allows them to carry at least moderate viral loads without apparent adverse effects.

In the new study, Dimopoulos and Dong examined the role of Argonaute 2 (Ago2), a protein that in mosquitoes serves as part of an important antiviral mechanism known as the small interfering RNA (siRNA) pathway, which works by recognizing and destroying viral RNAs.

The researchers found that in Ae. aegypti mosquitoes lacking the Ago2 gene, the siRNA pathway is impaired, arborvirus infection becomes more severe, and the mosquitoes' ability to transmit these viruses drops

sharply—as they sicken, feed less, and often die within days.

The scientists showed that this increased mortality is caused not only by the impairment of the siRNA antiviral pathway, but also by defects in two other processes that happen to depend on Ago2: DNA repair, and a basic waste-removal process called autophagy. Ago2-deficient mosquitoes exposed to arborviruses were left with hyperinfections, extensive DNA damage, and the accumulation of molecular waste in their dying cells.

Apart from illuminating an important aspect of Ae. aegypti biology, the findings point to a possible new arboviral disease control strategy. This would be to engineer the mosquitoes so that arbovirus infections trigger the loss of their tolerance mechanisms, perhaps via the inhibition of Ago2. Arborvirus-carrying Ae. aegypti mosquitoes would thus die quickly, whereas the much greater number of non-arborvirus carrying Ae. aegypti should be unaffected.

"The biology of mosquito susceptibility and tolerance to infection is an interesting area of exploration for other pathogens as well," says Dimopoulos. "For instance, mosquitoes that transmit malaria parasites could perhaps also be engineered to become sick and succumb to infection."

Dimopoulos and his research group are now exploring possible ways of engineering Ae. aegypti to test this possible new disease-control strategy.

More information: Shengzhang Dong et al, Aedes aegypti Argonaute 2 controls arbovirus infection and host mortality, *Nature Communications* (2023). DOI: 10.1038/s41467-023-41370-y

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