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Endogenous Retrovirus Activation in Pupal Fruit Flies May Boost Adult Antiviral Defenses

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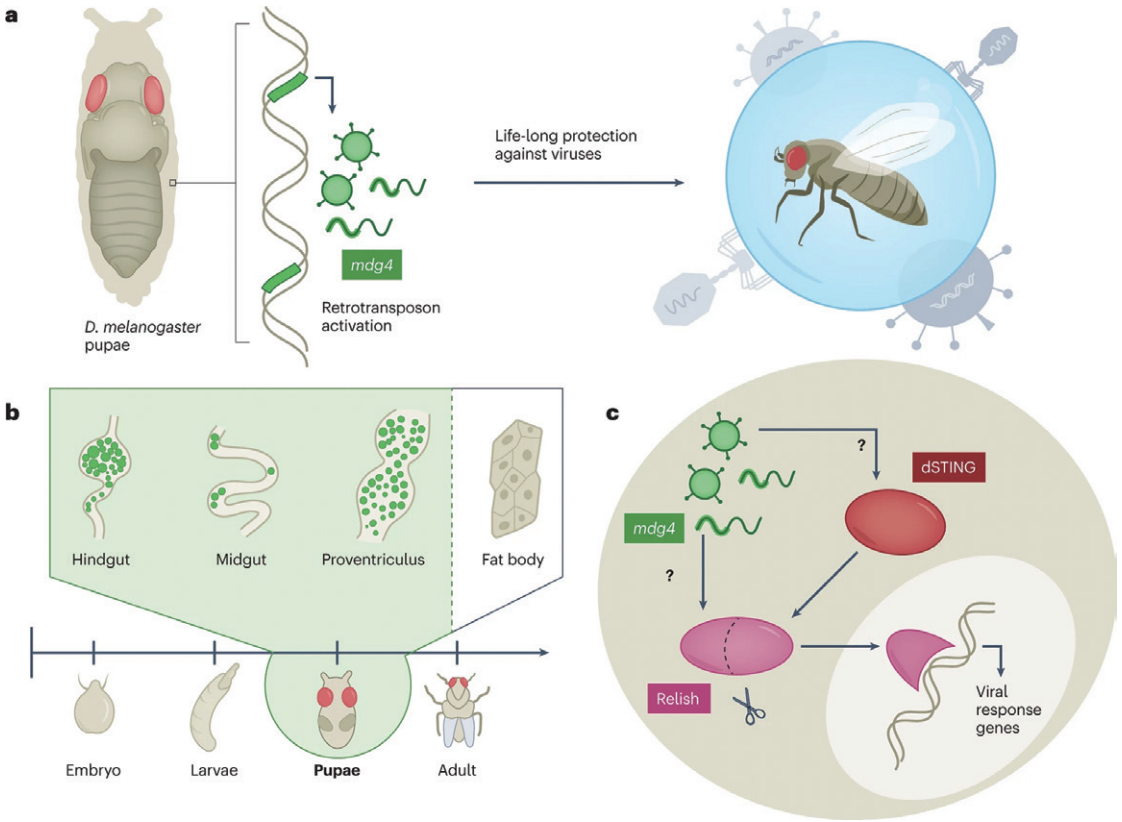
Recently, a research team jointly led by Dr. WANG Lu at the Shanghai Institute of Biochemistry and Cell Biology (SIBCB), Center for Excellence in Molecular Cell Science of the Chinese Academy of Sciences, and Dr. Z Z Zhao Zhang from the Duke University School of Medicine has found that the activation of the endogenous retrovirus (ERV) family *mdg4* in fruit flies during the pupal stage may enhance



Researchers have discovered the activation of the endogenous retrovirus (ERV) family *mdg4* at the fruit fly pupal stage may bolster adult antiviral defenses. a, Developmental *mdg4* expression increased adult protection against ingested viruses. b, Somatic retrotransposition of an *mdg4* reporter (eGFP$^+$ cells) was primarily found in the pupal-stage digestive tract. c, *mdg4* could stimulate Relish directly or via the dSTING sensor. (Image by Botto & Faulkner/*Nature Genetics*)

adult antiviral defenses. This groundbreaking research sheds light on the potential evolutionary benefits of ERV mobility in animals, which have previously been poorly understood.

The study, entitled "*Retrotransposon activation during Drosophila metamorphosis conditions adult antiviral responses*," was published online in *Nature Genetics* on November 17, 2022.

Transposable elements (TEs) are pieces of DNA that can copy or move themselves from one location in the genome to another. TEs are abundant in most animal genomes and can generate germline mutations.

While they are typically neutral or occasionally harmful to an organism's fitness, they can also provide some benefits. In the fruit fly *Drosophila melanogaster*, researchers discovered that the *mdg4* ERV family is active during the pupal stage, potentially helping to strengthen the adult fruit fly's antiviral defenses.

Drosophila melanogaster was chosen because it is an excellent model to observe and manipulate TE biology. The fruit fly has a variety of active TEs in both germline and somatic cells, which is useful for studying their role in immunity and other biological processes.

WANG *et al*. selected nine potentially mobile retrotransposon families, including *mdg4*, tagging them with an enhanced green fluorescent protein (eGFP) indicator cassette, and studying $eGFP^+$ cells in various adult tissues. As a result, they found a striking coincidence of *mdg4* transcription, virus-like packaging and retrotransposition in the pupal hindgut. Then, they investigated the biological function of *mdg4* activity, its relationship with mortality due to viral infection. Therefore , they found that the activation of the *mdg4* ERV family during this stage increased adult immunity to ingested viruses. Interestingly, they also revealed that fruit flies were more susceptible to viral infection if *mdg4* was silenced during the pupal stage, while *mdg4* knockdown in adults had no effect.

One possible explanation for these findings is that *mdg4* expression during the pupal stage helps prepare the adult fruit fly's immune system, rather than the mobility of *mdg4* itself.

The researchers suggested that *mdg4* may stimulate an immune response protein called Relish either directly or through the involvement of the dSTING sensor protein. Further research is needed to fully understand the mechanistic connections between *mdg4* and the immune response, as well as the cell-type specificity of *mdg4* activity in the developing hindgut.

This research raises important questions about the evolutionary role of TE mobility in somatic cells and its contribution to viral immunity among animals. The ability of still-mobile TEs to aid in immune system development could partly explain why total TE immobilization is rarely observed in animal germlines. Over time, TE families may be co-opted into other biological roles, perhaps initially being positively selected due to their antiviral properties.

While the study's findings are specific to fruit flies, they nonetheless reveal a fascinating new paradigm of developmental immune system training and offer valuable insights into the potential benefits of ERV mobility in animals.

References

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