CRISPR gene drives could eliminate many vector-driven pests and diseases, but challenges remain

A functioning gene drive system could fundamentally change our strategies for the control of vector-borne diseases by facilitating rapid dissemination of transgenes that prevent pathogen transmission or reduce vector capacity. CRISPR/Cas9 gene drive promises such a mechanism, which works by converting cells that are heterozygous for the drive construct into homozygotes, thereby enabling super-Mendelian inheritance.

Although CRISPR gene drive activity has already been demonstrated, a key obstacle for current systems is their propensity to generate resistance alleles, which cannot be converted to drive alleles. In this study, we developed two CRISPR gene drive constructs based on the nanos and vasa promoters that allowed us to illuminate the different mechanisms by which resistance alleles are formed in the model organism Drosophila melanogaster.

We observed resistance allele formation at high rates both prior to fertilization in the germline and post-fertilization in the embryo due to maternally deposited Cas9. Assessment of drive activity in genetically diverse backgrounds further revealed substantial differences in conversion efficiency and resistance rates. Our results demonstrate that the evolution of resistance will likely impose a severe limitation to the effectiveness of current CRISPR gene drive approaches, especially when applied to diverse natural populations.

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