Biotech In focus

Cooperative Extension Service
Biotechnology Outreach Program
College of Tropical Agriculture and Human Resources
University of Hawai'i at Manoa

July 2016 Issue 52

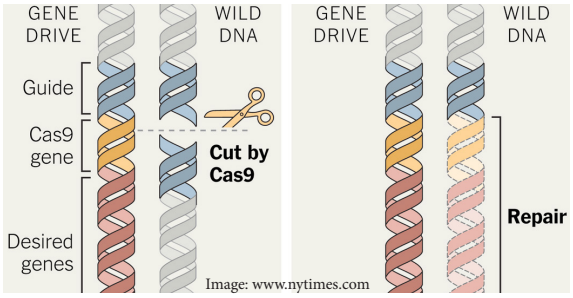
CRISPR-Cas9 and Gene Drives: The Risks and Benefits of Game-Changing Technology

Our past two bulletins introduced the gene-editing tool CRISPR-Cas9, a remarkable recent invention based on the virus-fighting defenses of bacteria. We've discussed how CRISPR can be used to very selectively cut and destroy (knock out) specific genes; the DNA recipes for making proteins. The resulting mutation—DNA sequence changes that can be inherited—prevent the damaged gene's protein from being made. This technology is of interest to agriculture because mutations can produce valuable new traits in crop plants. New traits (mutations) and natural variation are essential for successful breeding programs to develop new crop varieties. In this bulletin, we'll consider the other half of CRISPR's capacity for editing genes: its "paste" function, previously we spoke about stopping a gene's function.

When CRISPR-Cas9 cuts a cell's DNA, the cell has two different options for DNA repair. If no matching sequences of DNA are present, the broken DNA ends are stuck back together in an error-prone way that tends to knock out the damaged gene. However, if the cell contains DNA that matches and pairs with DNA sequences on either side of the CRISPR-Cas9 cut site, the broken DNA is swapped out, and the matched DNA helps replace it. This is called a gene knock-in as opposed to gene knock-out.

CRISPR-Cas9 knock-ins can be done quickly and cheaply. With knock-in gene editing, biotechnology research can advance at a faster rate. It will be easier to control the DNA sites at which new genes are added.

This technology, CRISPR-Cas-9, allows us to spread modified genes throughout populations of animals or plants. This process, known as a gene drive, would mimic the natural behavior of what are called selfish genes that are able to break DNA and copy or paste themselves into the break site.



Sexually reproducing animals have pairs of each chromosome, one from the female parent and one from the male. The selfish gene's DNA recipe makes a protein that cuts host cell DNA at a targeted site, allowing the selfish gene to jump into the broken chromosome during repairs. The selfish gene's protein cuts again, this time at the target site on the other chromosome of the pair. The DNA repair process uses the first chromosome (with its selfish gene) to repair the new cut. Now both chromosomes carry the selfish gene. Gene drives are based on this process of spreading a gene not only from one generation to the next, but also within each generation.

For more information and past issues, please visit our website at www.ctahr.hawaii.edu/biotechinfocus

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Thank you to Jessica Radovich for graphics and Kathleen Vickers for text editing.

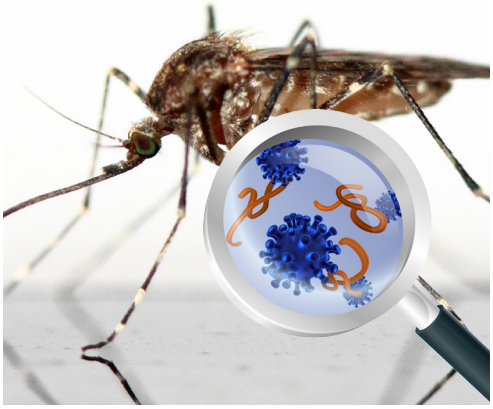
Focusing Gene Drive Research

If a selfish gene is added to an animal's reproductive cells, nearly all of the animal's offspring will inherit the selfish gene. (By comparison, if the gene was playing by the usual rules of inheritance, only half of the offspring would get a copy.) This process repeats in the offspring as well, so that almost all of their offspring receive the selfish gene. In just a few generations, the selfish gene could spreads through the population.

One focus of gene drive research is the mosquito that transmits malaria. Malaria each year sickens more than 200 million people and kills more than 400,000. Additional candidate species for this approach include mosquitoes that spread other diseases, such as Zika virus and dengue, and the tick that carries Lyme disease.

Advancing Research

As research advances, technical and ethical questions arise. Should CRISPR-Cas9 be used to drive disease-spreading insects toward extinction? Would that approach speed up the development of insect resistance to the gene drive? Can this technology target the microbes within the pests, rather than the pests themselves, so that the pests can't transmit disease but don't evolve resistance? In that case, how will the microbes evolve in response?



Human Application

As CRISPR technology is further refined and applied to human health issues, we will face new challenges in medical ethics. Should we limit gene therapies to treating individuals, or should we modify human germ lines—the cells that give rise to our children and later generations—to eliminate mutations that cause terrible diseases? Is it more important to prevent the future suffering of patients or to ensure against the misuse of human germ line engineering by banning the practice?

A Natural Mechanism

CRISPR-Cas9 gene drives offer great potential benefits—preventing diseases, suppressing invasive species, perhaps reversing evolved resistance to pesticides. These technologies also carry significant potential risks, such as accidental release of a gene drive or unintended effects that gene drives might produce in individuals and ecosystems. Unlike genetically modified crops, gene drives are built to spread in the environment. Gene drive is one of the natural mechanisms involved in the evolution of plants and animals.

A major question that needs to be discussed as we work through the benefits and risks of this technology is: Can different nations agree on how they should be used, knowing that the genes will cross political borders? Genes do not see National borders as barriers to movement and they need to provide a selected advantage to an individual plant or animal for it to survive and reproduce in a new area. All of us—researchers, regulators, and communities worldwide—now face decisions that were difficult to imagine 20 years ago.

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