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Gene drives and the management of agricultural pests

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Gene drives and the management of agricultural pests

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ABSTRACT
Gene editing using CRISPR-Cas9 provides potential for novel ways of genetic pest control by improving gene drives. Like all pest control strategies, gene drives are not hazard-free. Difficulties involved in the containment of gene drives may restrict their use and require international agreements before release of approved types. Ecological risk assessment of gene drives designed to control agricultural pests should be conducted before their deployment. Public support will be crucial for the implementation of gene drives for pest control. Natural and social scientists need to work together to design ways to include the public in the decision-making process. The present commentary provides some thoughts on some of the issues one should consider when contemplating using gene drives in the management of agricultural pests.

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Introduction

Improvements in gene editing through the use of CRISPR-Cas9 have provided venues to develop novel solutions to old problems (Doudna and Charpentier 2014). CRISPR-Cas9-based gene editing has already provided hope in the treatment of HIV (Kaminski et al. 2016), as well as promised to offer a new generation of sickle-cell anemia, hemophilia and cancer treatments (Carroll 2014; Kannan and Ventura 2015; Liu et al. 2016; Tang and Shrager 2016). It has shown potential ways to diminish the human suffering caused by malaria and other vector-borne diseases (Ghorbal et al. 2014; de Koning-Ward, Gilson, and Crabb 2015; Hammond et al. 2016), as well as impacted animal and plant breeding (Jenko et al. 2015; Weeks, Spalding, and Yang 2016). In agriculture, gene editing may significantly improve gene drives used for pest control.

Gene drives consist of genetic elements that are efficiently transmitted among sexually reproducing individuals, even if they reduce an organism's fitness (Esvelt et al. 2014; Hammond et al. 2016). Thus, gene drives can pass traits with higher efficiency than expected under Mendelian inheritance (Esvelt et al. 2014; Dance 2015). Although the use of gene drives for pest control has been seriously considered for over a decade (Curtis 1994; Spielman 1994; Davis, Catchpole, and Fulford 2000; Davis, Bax, and Grewe 2001; Burt 2003; Burt and Koufopanou 2004; Schliekelman, Ellner, and Gould

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2005; Sinkins and Gould 2006; Bax and Thresher 2009), its implementation was not straightforward. CRISPR-Cas9-based gene editing has changed that. Thus, although there have not been any releases of gene drives yet, it may be a matter of time before several agricultural pests and natural enemies become potential candidates for carrying gene drives (Gurr and You 2016; Scott et al. forthcoming). However, not all pest species are suitable for control using gene drives. In order for gene drives to work, pests need to reproduce sexually and have short generation times. The effectiveness of gene drives deployed for pest control will also depend on the breeding structure of the target pest as well as on its geographic distribution and degree of gene flow (NASEM 2016). Thus, not all pest species may be suitable for control using this technology. Nevertheless, the use of gene drives for pest control of suitable pest candidates calls for a full consideration of the hazards involved in their deployment.

The National Academies of Sciences, Engineering and Medicine released a report outlining the hazards to be considered when thinking about gene drives (NASEM 2016). In addition, the United States (US) is currently engaged in modernizing its coordinated framework for the regulation of biotechnology (Waltz 2015; Executive Office of the President 2016, 2017; Kuzma 2016). It is expected that the modernized framework will take into consideration the likelihood associated with the hazards involved in pest control using gene drives. In this brief commentary, I offer just an example of the kind of issues one should consider when thinking about using gene drives against agricultural pests.

Pest elimination and potential hazards

In theory, traits introduced using gene drives could be designed to spread to fixation from a single individual (Burt 2003). This sort of gene drive, also referred to as global gene drive (Esvelt, personal communication), could result in local or even global pest extinctions (Oye et al. 2014). The spread of global gene drives could be stopped, at least in theory, using reversal or immunization gene drives (Esvelt et al. 2014). However, the effectiveness of these remediation strategies is still theoretical, and any ecological damage caused by the release of inadequate gene drives might be irreversible (Esvelt et al. 2014; Akbari et al. 2015). Some people may find global gene drives appropriate as part of eradication programs. However, the prospect of humans purposely causing the extinction of another species brings about several novel angles to pest control. The pest concept is an anthropocentric construct. Pests are defined as species that happen to use resources we use and whose numbers grow above a threshold that is economically damaging. Prior to considering the use of global gene drives for pest control, key questions should be answered. For example, what will the ecological consequences of pest species extinctions be? How many species can we eliminate before facing serious consequences? Who will decide which species deserve to be driven to extinction? Is it ethical for humans to decide which species should go extinct?

The elimination of native agricultural pest species (like the Colorado potato beetle in North America) could have unintended ramifications. We currently lack the ability to fully predict the consequences of species extinctions. Consequently, it would be wise to place an international moratorium on the deployment of global gene drives for pest control until their potential risks are better assessed. The definition of risk is context dependent. Colloquially, risk is understood as threat or hazard. However, when the term is used in ecological risk assessments, it acquires a probabilistic meaning (Suter 2007). The recent NASEM report on gene drives defines risk as 'the probability of an effect on a specific endpoint or set of endpoints due to a specific stressor or set of stressors' (NASEM 2016), where endpoints represent the values to be protected (Suter 2007). Risks associated with global gene drives may be too high for their deployment. Fortunately, there are less risky kinds of gene drives: for example, temporary gene drives or gene drives that activate only after specific thresholds or environmental conditions are reached (Alphey and Andreasen 2002). This latter kind, also referred to as local gene drives (Esvelt, personal communication), can be incorporated into current integrated pest management (IPM) programs with a lower risk than global gene drives. Nevertheless, the NASEM report on gene drives considered that currently there is not enough information to support the release of gene drives in the environment (NASEM 2016).

In the future, when more knowledge accumulates and ecological risk assessments are conducted on gene drives, it may be advisable to temporarily restrict the use of local gene drives to control only recently invasive agricultural pest species. They could be used as part of area-wide invasive pest suppression programs (Myers et al. 2000). If local gene drives succeed in suppressing recent invaders (like *Drosophila suzukii* in the US), it is likely that they will also be used to control older invasions (like the European corn borer, *Ostrinia nubilalis*, in US maize). Time since invasion is an important consideration. While recent invaders could be locally or even regionally suppressed without much ecological cost, things may go differently for established invasive species. Established invasive pests may have displaced their native competitors taking their ecological roles (LeBrun, Abbott, and Gilbert 2013), making their eradication problematic due to the unknown consequences of empty niches. In such instances, use of local gene drives may require accompanying restoration strategies. In several instances, invasive species may have established in wild habitats before being noticed in crops, making time since invasion difficult to estimate. A proper ecological risk assessment will require provisioning local, state and national regulatory agencies with funding to conduct thorough environmental impact assessments in locations under pest control using local gene drives.

Local gene drives should first be tested and monitored on islands. Although organisms carrying local gene drives may still escape from islands, the isolation provided by islands may add an extra level of containment (O'Connor et al. 2012). Local gene drives could also be restricted by functioning only on specialized pests (e.g. western corn rootworm, *Diabrotica virgifera*, feeding on European corn) or in generalist pests but only when feeding on a specific crop (e.g. cotton bollworm, *Helicoverpa armigera*, feeding on corn). Theoretically, future gene drives could be designed to work only when specific components of the diet are present, like for example in a specific crop variety. The deployment of local gene drives in relatively contained habitats will allow data gathering on their effectiveness while increasing our ability to correct any unintended consequences. If successful, data generated by these prototype control efforts will ease conversations with stakeholders and the public and inform collective decision-making involving local gene drives. Later generations of local gene drives could target less isolated invasive pests. In addition, since it is highly likely that containment efforts will fail, it is important to have strategies in place to prevent local gene drives from spreading out of control. It is also important that the regulation of local gene drives requires precision gene drives or the creation of tested reverse or immunization gene drives before getting approval for deployment (Esvelt et al. 2014; Oye et al. 2014).

Further, the long-term effect of local gene drives on target species diversity should also be assessed (Oye et al. 2014). To mitigate the effects of any potential biodiversity losses, regulatory agencies should require protocols for genomic preservation of pest populations to be controlled using gene drives. Ideally, representative genomes of pest populations should be kept in government-run genomic libraries. We already have similar infrastructures to preserve plant material (Hopkin 2008). Pest population genomic banks may come in handy if accidental extinctions occur. Besides easing our fears of losing genomic information, future generations might be able to de-extinct or resurrect species eradicated by mistake (Thompson 2015). In addition, organisms classified as pests by some groups may be of value to others (Turner 1985). Due to this and the likelihood of local gene drives spreading beyond their intended area of action, their regulation should require public discussion and, when appropriate, international agreements. For example, salt cedar is considered a pest by landowners but a valuable tree by wildlife protection groups (Dudley and Bean 2012). Similarly, prickly pear is considered a pest in Caribbean countries but a valuable plant in Mexico (Zimmermann, Klein, and Bloem 2004; Zimmermann, Bloem, and Klein 2007). Aided by hurricanes, biocontrol agents released in the Caribbean region to control prickly pear have reached Mexico (Andraca-Gómez et al. 2015). International regulation of local gene drives may impede their release when faced with these sorts of situations.

Pest population modifications

Another function of gene drives could be to eliminate pesticide resistance (Esvelt et al. 2014). Since pesticide resistance is already a consequence of human intervention, using gene drives to revert it seems less controversial. However, without the threat of resistance, indiscriminate use of pesticides may ensue in some agricultural systems or cultures. Regulations will be needed to prevent these scenarios. Moreover, governments may require pesticide companies to have strategies in place for the design of local gene drives to revert resistance to their products before granting registrations. Products in which resistance cannot be reverted could then be discontinued. Another interesting application of gene drives could involve their use to spread pesticide resistance genes in wild populations. For example, milkweeds able to tolerate herbicides could prevent monarch butterfly populations from declining. Similarly, gene drives could protect bees by making them resistant to certain pesticides in situations in which insecticide use could not be avoided. But before these types of gene drives get approved, the hazard of horizontal gene drive transfer should be thoroughly investigated. It is important to be aware that the use of this remediation approach is not enough to protect wildlife biodiversity. Targeting one or two charismatic or beneficial species will not be an ideal solution. Thus, implementation of this strategy should only be allowed in situations in which pesticide elimination is unavoidable.

Alternatively, gene drives may involve modifying pests' ability to host key symbiotic microorganisms. Obligate and facultative symbioses with bacteria are common in several arthropod pests (Bourtzis and Miller 2003; Oliver et al. 2010). For example, aphids cannot survive without the symbiotic bacteria, *Buchnera aphidicola* (Douglas 1998). Gene drives could spread genes designed to prevent aphids' ability to host-specific symbiotic bacteria. Similarly, gene drives could spread genes designed to eliminate vector competence in arthropod species that transmit plant diseases. Because eradicating microorganisms may have unintended consequences in some systems, pest control using gene drives to interfere with the ability of arthropods to host or vector microorganisms should also require archival of microorganisms' genomic material.

Summary

The incorporation of gene drives into pest control practices will require public support as well as ample discussion among stakeholders. Ecological and evolutionary considerations similar to the ones addressed in this brief commentary should be part of the conversation. On the other hand, the current national and international regulatory landscape will need to be updated so it can harvest gene drives' potential while mitigating the hazards involved in their deployment. Several countries, including the US, are modernizing their regulations to incorporate gene drives and other novel pest control technologies (Waltz 2015). Too little regulation may translate into serious risks, alternatively too much regulation may delay scientific progress and impact economic growth. It is important to consider that currently used pest control practices are not risk-free (Oye et al. 2014). Thus, the incorporation of gene drives in some scenarios may actually reduce risks when compared with currently adopted practices. Gene drives will not provide us with silver bullets; instead, they will likely be integrated into current IPM programs. The hazards of using gene drives might prevent their implementation in some situations while their benefits might justify their use in others. Decisions regarding when to use gene drives should be informed by the findings of both natural and social sciences.

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Disclosure statement

No potential conflict of interest was reported by the author.

Notes on contributor

Dr Raul F. Medina's research interests center around the role that ecological factors play in the population genetics of arthropods. Dr Medina is particularly interested in the incorporation of evolutionary ecology considerations into pest control practices. His laboratory is currently assessing how species interactions at macroscopic (e.g. host–parasite associations) and microscopic (e.g. arthropod microbiomes) levels may affect genetic variation of agricultural pests and arthropod vectors of human disease. Dr Medina is currently exploring if the same principles governing insect herbivores' adaptation to their hosts translate in arthropod parasites of animals. Dr Medina completed his Bachelor in Biology in Lima, Peru at the Universidad Nacional Agraria La Molina. He then obtained a Graduate Certificate in conservation biology from the University of Missouri in Saint Louis. He received his Master and Ph.D. from the University of Maryland

working on predation of forest caterpillars and on hymenopteran parasitoid population genetics, respectively. Soon after his Ph.D., Dr Medina started working at Texas A&M where he is currently a Professor.

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