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Commentary

The Development and Testing of Synthetic Gene Drives Based on CRISPR-Cas9 Technology

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DESCRIPTION

Synthetic gene drives are genetic engineering tools that can bias the inheritance of specific alleles or traits in a population, allowing them to spread rapidly and persistently. Synthetic gene drives can be used to modify or control target populations for various purposes, such as pest management, disease prevention or conservation. CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats) is a genome editing technology that can be used to create synthetic gene drives by introducing targeted double-strand breaks in the DNA and inducing homology-directed repair. CRISPR-Cas9-based synthetic gene drives consist of three main components: a Cas9 nuclease that can cut DNA (Deoxyribonucleic Acid) at a specific site, a guide RNA (gRNA) that directs Cas9 to the target site, and a drive allele that contains the desired modification and the Cas9-gRNA cassette. The drive allele is designed to replace a wild-type allele on the homologous chromosome by copying itself during DNA repair. This process can increase the frequency of the drive allele from 50% to nearly 100% in each generation, resulting in its eventual fixation in the population.

Synthetic gene drives can be classified into two main types: suppression drives and modification drives. Suppression drives aim to reduce or eliminate the target population by inducing sterility, lethality or reduced fitness. For example, a suppression drive can target an essential gene for normal development or reproduction and disrupt its function. Modification drives aim to alter the target population by introducing a beneficial trait or removing an undesirable one. For example, a modification drive can target a gene involved in pathogen transmission and replace it with a resistant allele.

The development and testing of synthetic gene drives based on CRISPR-Cas9 technology have been mainly focused on insects, especially mosquitoes that transmit malaria, dengue and zika. Several proof-of-concept studies have demonstrated the feasibility and efficiency of CRISPR-Cas9-based synthetic gene drives in laboratory settings, using model organisms such as *Drosophila melanogaster*, *Anopheles gambiae* and *Aedes aegypti*. However, there are still many challenges and uncertainties for the application of synthetic gene drives in natural populations, such as genetic variability, resistance evolution, ecological interactions and ethical implications.

Genetic variability refers to the diversity of genotypes and phenotypes in the target population, which can affect the performance and spread of synthetic gene drives. For example, genetic variability can result in mismatched gRNAs that fail to recognize or cut the target site, leading to reduced efficiency or off-target effects. Genetic variability can also result in pre-existing or de novo resistance alleles that escape or counteract the drive mechanism, leading to reduced efficacy or reversal of the drive. Therefore, it is important to assess and monitor the genetic variability of the target population before and after deploying synthetic gene drives.

Resistance evolution refers to the emergence and spread of resistance alleles that confer an advantage over drive alleles in terms of fitness or transmission. Resistance evolution can occur through various mechanisms, such as Non-Homologous End Joining (NHEJ), Alternative End Joining (A-EJ), Homologous Recombination (HR), and maternal deposition of Cas9 inhibitors or natural selection. Resistance evolution can limit or compromise the effectiveness and durability of synthetic gene drives. Therefore, it is important to design and test synthetic gene drives that can minimize or overcome resistance evolution.

Ecological interactions refer to the effects of synthetic gene drives on the target population and its associated species and ecosystems. Ecological interactions can be positive or negative, direct or indirect, intended or unintended. For example, synthetic gene drives can reduce the burden of vector-borne diseases on human health and well-being, but they can also alter the ecological roles and functions of the target species and its predators, prey, competitors and symbionts. Therefore, it is important to evaluate and predict the ecological interactions of synthetic gene drives before and after releasing them into the environment.

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Ethical implications refer to the moral and social issues raised by synthetic gene drives regarding their purpose, process and outcome. Ethical implications can involve various stakeholders, such as researchers, regulators, funders, communities and publics. For example, synthetic gene drives can raise questions about their safety, efficacy, necessity, acceptability, accountability and governance. Therefore, it is important to engage and consult with diverse stakeholders about synthetic gene drives before and during their development.