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Targeted Remodeling of Bacterial Genomes Using CRISPR-Nickases

Targeting DNA manipulation is integral to biotechnology and synthetic biology. Large chromosomal rearrangements and deletions have profound impacts on bacterial physiology, such as improved bioproduct levels, increased strain fitness, or changed tolerance to stress and environmental conditions. However, it requires time-consuming and laborious directed evolution experiments to produce these genotypes.

Programmable clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-Cas systems have enabled accurate yet small-scale genomic manipulations, however, their potentials to engineer large-scale remodeling of bacterial genomes have not been explored. Efficient methods to target this process for large-scale genome manipulations would be beneficial to biotechnology.

Researchers at Arizona State have developed novel methods to direct multiplexed large-scale genomic recombination using CRISPR-targeted nickases in Escherichia coli. CRISPR-guided nickase systems can be programmed to make precise, non-lethal, single-stranded incisions in targeted genomic regions. They have demonstrated that dual-targeted nicking enables deletion of 36 and 97 Kb of the genome. Furthermore, multiplex targeting enables deletion of 133 Kb, accounting for approximately 3% of the entire E.coli genome.

This technology provides a framework for the construction of genetic devices to direct accurate and large-scale genome remodeling and facilitates prokaryotic chromosomal modifications which could be incredibly beneficial to biotechnology.

Potential Applications

• Novel tool for designing and engineering bacterial genomes

o Target recombination between homologous DNA sequences

o Applied for increased production of useful chemicals, and products

o Engineer growth and proliferation of bacteria

o Genome editing for bacterial genetic research

o Development of microbes with increased tolerance to stress and adverse

environmental conditions

Benefits and Advantages

• Removal of genomic segments in targets and the execution is controlled

• Could be used in rationally designed and multi-targeted removal of pathways competing with the production of useful chemicals or factors reducing growth

• This system can be targeted with high versatility

• This system is desirable to synthetic biology applications

• Can work synergistically with preexisting bacterial genome engineering systems

For more information about the inventor(s) and their research, please see Dr. Wang's laboratory webpage