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Compact Effector Domains for Activating and Silencing Gene Expression

Researchers at Stanford have developed a new catalog of compact transcription effector domains and fused them onto DNA binding domains to engineer synthetic transcription factors. These synthetic transcription factors can perform targeted and tunable regulation of gene expression in eukaryotic cells, with applications in gene and cell therapy, synthetic biology, and functional genomics. Previously, a limited number of effector domains were available for engineering synthetic transcription factors. To address this limitation, the researchers developed the new, high-throughput approach to discover and characterize effector domains. Their approach has enabled the discovery of hundreds of short effector domains (?80 amino acids; advantageous for delivery) that can upregulate or downregulate transcription in a targeted manner when fused onto a DNA binding domain. This process can also identify mutants of effector domains with enhanced activity.

Stage of Development
The collection of domains identified by the researchers is large and diverse, and the platform readily enables new combinations of domains to be tested as fusions in high-throughput to create synthetic transcription factors with new properties.

Applications

- Targeted repression/activation of endogenous genes
- Gene and cell therapy
- Synthetic transcription factors can be used to perturb the expression of multiple genes simultaneously (e.g., high-throughput genetic interaction mapping with CRISPRi/a screens using multiple guide RNAs).

- Use in synthetic transcription factors in genetic circuits, e.g., inducible gene expression or more complex circuits

Advantages

- Minimally sufficient sequences (e.g., 10 amino acids) are an advantage for delivery (e.g., packaging in viral vectors)
- Domains extracted from human proteins reduce immunogenicity in compared to viral effector domains.
- Most of the domains generated have NOT previously been reported as transcriptional effectors
- High throughput

Publications

- Josh Tycko et al High-Throughput Discovery and Characterization of Human Transcriptional Effectors *Cell* Dec. 23, 2020.

Patents

- Published Application: WO2021226077
- Published Application: 20240401032

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