GBSBC

Genetics, Bioinformatics, & Systems Biology Colloquium

presents

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THURSDAY
MAY 25

12PM

LEICHTAG
AUDITORIUM

ZOOM

JOIN

ROBUST EPIGENOME EDITING TECHNOLOGIES FOR DISSECTING GENE REGULATORY MECHANISMS AND ENGINEERING HUMAN CELLS

Recent advances in CRISPR/Cas-based technologies have enabled programmable control over human gene expression, chromatin states, and genomic organization. Thus, these emerging technologies hold tremendous promise for functionally dissecting complex gene regulatory mechanisms in situ. In addition, these tools have created new opportunities to engineer human cells to meet basic and applied research needs. Toward these ends, we have recently developed new capabilities in the context of CRISPR-based transcriptional activation (CRISPRa). First, wehave sourced key segments from native human transcription factors to build potent and compact multipartite transactivation modules and in turn build the CRISPR-DREAM platform. CRISPRDREAM is specific, robust across mammalian cell types, efficacious at diverse regulatory elements, and well tolerated in therapeutically important primary cells, such as T cells, MSCs, neurons, and iPSCs. We have also leveraged the small size and potency of CRISPR-DREAM components to build new all-in-one CRISPRa AAV systems that expand opportunities for in vivo gene control. Second, we have isolated intrinsically disordered regions (IDRs) from oncogenic fusion proteins known to be associated with nuclear phase separation and hematologic malignancies. We find that different IDR compositions exhibit distinct propensities for nuclear import and biomolecular condensation in human cell nuclei. We also demonstrate using CRISPRbased targeting of IDRs, that levels of phase separation can be directly proportional to target gene activation. Interestingly we also find that while core transcriptomic changes are shared among certain oncogenic IDR fusion proteins, phase separation behaviors and genomic engagement occur in discrete ways, suggesting divergent mechanistic routes to cellular oncogenesis.

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