Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad – 500 046

Webinar

On-demand genome folding using a novel optoepigenetic tool

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Genome topology - how the DNA is folded in a cell in 3D – is intimately linked to turning genes on/off. Improper 3D genome organization can cause misregulation of genes and lead to defects during development and cancer. Yet, in a majority of cases, we do not know which of these tens of thousands of genome contacts are functionally important and causally affect transcription of genes. Moreover, the dynamics of these genome contacts on short time scales remains a fundamental unanswered question. Published strategies for loop engineering involve use of zinc fingers or synthetic transcription factors tethered to dCas9, which are always turned on or induced on long time scales using small molecules. The paucity of tools to engineer genome folding on short time scales has prohibited scientists' ability to understand the extent to which loops are dynamic and functionally contribute to the kinetics of transcriptional activation. I will discuss a new class of 3D optoepigenetic tools for the directed rearrangement of 3D chromatin looping on short time scales using light. We target our light-activated-dynamic-looping (LADL) system to two genomic anchors with CRISPR guide RNAs and induce their spatial colocalization via light-induced heterodimerization of cryptochrome 2 and a dCas9-CIBN fusion protein. We applied LADL to redirect a stretch enhancer (SE) away from its endogenous Klf4 target gene and to the Zfp462 promoter in mouse embryonic stem cells. LADL facilitates colocalization of genomic loci without exogenous chemical cofactors and will enable future efforts to engineer reversible and oscillatory loops on short time scales.

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