LADL : Light-Activated Dynamic Looping and its functional effects

Ji Hun Kim, Ph.D

Korea Advanced Institute of Science and Technology (KAIST)

Abstract

Mammalian genomes are folded into tens of thousands of long-range looping interactions. The cause-and-effect relationship between looping and genome function is poorly understood, and the extent to which loops are dynamic on short time scales remains an unanswered question. Here, we engineer a new class of synthetic architectural proteins for directed rearrangement of the three-dimensional genome using blue 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 apply LADL to redirect a stretch enhancer (SE) away from its endogenous Klf4 target gene and to the Zfp462 promoter. Using single-molecule RNA–FISH, we demonstrate that de novo formation of the Zfp462-SE loop correlates with a modest increase in Zfp462 expression. 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.