Docket #: S18-365

CRISPR-GO: A Method for Programmable Genome Re-organization

Researchers at Stanford have expanded the CRISPR method to enable programmable, targeted control of spatial genomic DNA organization in the nucleus and allow for regulated gene expression over a long distance. The spatial organization of the genome in the nucleus is important for regulating gene expression, maintaining genome stability and cellular function. Further, the nucleus possesses many subnuclear compartments that are thought to play a role in genome organization and function. Understanding the relationship between genome structure, its organization within nuclear compartments and how this effects gene expression can provide insights into many biological processes. To aid this understanding the inventors have developed this versatile system for programmable genome reorganization named CRISPR Genome Organizer (CRISPR-GO). Here, the inventors have coupled the CRISPR-dCas9 system with nuclear compartment-specific proteins via a chemically inducible dimerization system to enable programmable targeted control of genomic DNA interactions with various nuclear compartments. The CRISPR-GO system expands the CRISPR gene editing and regulation capabilities. It can be used as a research tool to study the functional role of spatiotemporal genome organization and for genome engineering.

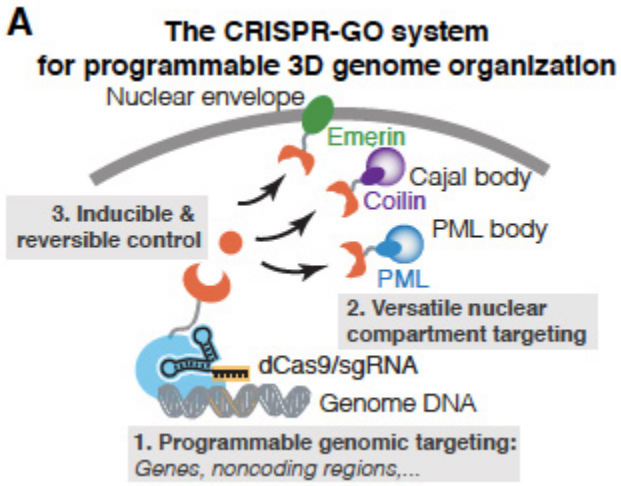

Image courtesy the Qi Lab

Schematic of CRISPR-GO. dCas9 and a nuclear compartment-specific protein are fused to complementary pairs of heterodimerization domains, which assemble only in the presence of a chemical inducer. The genomic targets are specified by the sgRNA sequences and nuclear compartments are programmed by fusing CRISPR-GO with compartment-specific molecules.

Stage of Development –Research In Vitro

The inventors have shown that CRISPR-GO allows efficient, inducible, and dynamic re-positioning of genomic loci to the nuclear periphery, Cajal bodies, and PML nuclear bodies. Further, they found that co-localization of genomic loci with certain nuclear bodies repressed expression of adjacent genes across long distances.

Applications

- Genomic engineering
- Distal gene regulation
- Research tool: study functional role of spatiotemporal genomic organization in gene regulation, genome stability and cellular function, and study real-time dynamics of chromatin interactions with nuclear compartments.

Advantages

- First use of CRISPR for macro-scale genomic engineering
- Programmable, inducible, and reversible
- Enables interrogation of real-time dynamics of chromatin interactions with nuclear compartments in living cells
- Allows investigation of large-scale genome organization and function in a targeted manner
- Allows programmable re-localization of genomic loci in a precise and targeted manner
- Can target repetitive and non-repetitive chromatin loci located on different chromosomes to nuclear compartments
- Can be expanded to target additional nuclear compartments

Publications

- Wang, H., Xu, X., Nguyen, C. M., Liu, Y., Gao, Y., Lin, X., Daley, T., Kipniss, N.H., La Russa, M. and Qi, L.S. (2018). CRISPR-mediated programmable 3D genome positioning and nuclear organization. *Cell, 175*(5), 1405-1417.
- Qi, L. S., & Wang, H. (2022). *U.S. Patent Application No. 17/180,535*.

Patents

- Published Application: WO2020041679

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