HiCAR: An assay that can expand ability to study chromosome structure and interactions for identifying new therapeutic targets

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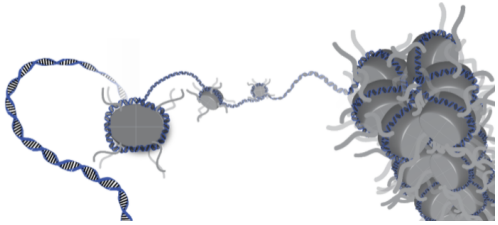

Unmet Need

More than 98% of the human genome are non-coding sequences, and the vast majority (~93%) of human disease and associated risk variants lie in these non-coding regions. These previously regarded non-essential regions in the genome are now supported by a growing body of evidence to contribute to various developmental processes and human diseases, including cancer. The regulatory sequences of the genome are often the “open” or accessible sequences of DNA, and can be measured genome-wide by assays such as ATAC-seq, DHS-seq, or FIRE-seq, etc. However, the ability to study the way that cis-regulatory sequences contribute to development and human disease remains challenging, as most of the regulatory sequences are controlling the expression of distal genes that could be hundreds of kilobases or even millions of bases away. Hence, a robust, sensitive, and cost-effective method is urgently needed for the analysis of cis-regulatory chromatin organization, so we can identify new therapeutic targets that are regulated by distal cis-regulatory sequences carrying the disease-causing variants. The currently available research tools, such as chromosome conformation capture (3C) based assays, either require ultra-deep sequencing depth and expensive to reveal high-resolution chromatin organization (Hi-C, Micro-C), or require pairing with specialized antibodies (HiChIP, PLAC-seq) or pre-designed oligo probes (capture-C) to capture only a subset of protein-centric or probe-centric chromatin interactions, or can’t be applied to low input samples such as clinical samples or primary cells purified from animal models. Additionally, none of the available technologies enable simultaneous assessment of the transcriptome from the same biological sample. There is a need for improved tools for studying chromatin structure and interactions to enable the identification of new therapeutic targets.

Technology

Duke inventors have reported an assay to support the

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Links

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identification of novel therapeutic targets and to overall better understand human diseases. Specifically, HiCAR (***Hi***gh-throughput ***C***hromosome conformation capture on ***A***ccessible DNA with m***R***NA-seq co-assay) is a method that enables simultaneous assessment of *cis*-regulatory chromatin interactions and chromatin accessibility, as well as evaluation of the transcriptome, which represents the functional output of chromatin structure and accessibility. A prototype has been developed and demonstrated to produce a 17-fold greater yield of informative long-range *cis*-reads at a similar sequencing depth and required 1,000-fold fewer cells as input when compared to Trac-looping, another currently available method. This technology was successfully used to analyze *cis*-regulatory chromatin interactions in mouse and human embryonic stem cells.

Advantages

- Does not require target-specific antibodies like immunoprecipitation-based methods including HiChIP, PLAC-seq, ChIA-PET
- Does not require pre-designed capture probes like Capture-C
- Better captures long-range physical interactions than Trac-looping
- A need for fewer input cells (50-100 thousand cells) makes this compatible for assessing clinical samples
- Cost-effective – identifies high-confident interactions at 10kb resolution and 5kb resolutions with 300M and 600M raw reads (200M and 400M uniquely mapped reads), respectively
- Can be considered as the “ATAC-seq” version of HiChIP or PLAC-seq

Publications

- Multi-omics analysis of chromatin accessibility and interactions with transcriptome by HiCAR (bioRxiv, 2020)
- Analysis of cis-regulatory chromatin contacts anchored on open DNA sequences by HiCAR (4D Nucleome Scientific Webinar Series, 2021)