Chromatin Immuno-Methylation Sequencing (ChIME-seq)

Potential impact

ChIME-seq is a novel workflow which uses a targetable GpC methyltransferase to simultaneously detect endogenous DNA methylation and a DNA proximal target (e.g. histone modifications) genome wide. It also offers a readout of nucleosome positioning and chromatin accessibility within target regions. Results link all modalities within the same single-cell and single-molecule enabling direct inspection of both the spatial and temporal relationships between them. Downstream processing is flexible for the end user as any existing cytosine methylation sequencing method may be applied to the cell preparation as desired. This includes any or all of bulk, long-read and single-cell readouts from a single experiment in either a genome-wide or locus-specific manner.

Key advantages

- Multiple epigenetic modalities identified directly through the same single-molecule and single-cell, allowing the direct study of spatial and temporal relationships between epigenetic marks.
- Flexibility of downstream application – use of targeted cytosine methylation allows long-read, short-read and single-cell processing, genome-wide or locus-directed, using established protocols and analysis pipelines from a single cell preparation.
- Much higher on-target signal versus DiMeLo-seq and signal:noise versus Cut&Tag-BS, with the refined protocol.
- Reproducible and robust – protocol replicated from written format, without tuition or oversight, by collaborators.
- Potential use in targeting or footprinting of transcription factors.
- Inclusion of transcriptome in testing with promising initial results.
Fig. 1 Workflow and Experimental Results

A. Schematic overview of (I.) the ChIMe-seq workflow and (II.) the downstream sequencing options. B. An IGV genome browser view of ChIMe-seq results for different histone modification targets and corresponding ChIP-seq results. ChIP-seq and WGBS results are taken from ENCODE. ChIMe-seq DNAme shown is from the H3K27me3 sample. All samples are displayed in 1kb bins with y-axis units of methylation $\beta$ for methylation measurements and read-counts for ChIP-seq.
Fig. 2 ChIMe-seq methylation data

A. Heatmap of pearson correlation values between each sample shown in Fig 1. B-D Examples of scatter plots underlying correlation results shown in A, again in 50kb bins. (B) CG methylation β from ChIMe-seq Vs WGBS, (C) ChIMe-seq GC methylation β Vs ChIP-seq counts (H3K27me3 target) (D) CG methylation β Vs GC methylation β from a single ChIMe-seq experiment (H3K27me3 target). E. Percentage of targeted signal (individual /non-aggregated methylated GC calls for ChIMe-seq, read-counts for ChIP-seq) found within peaks generated from ChIP-seq data. F. Percentage of individual GC calls called methylated within peaks generated from ChIP-seq data. G-H Scatter plots of methylation β in 50kb bins showing reproducibility of ChIMe-seq. (G) Reproducibility of CG methylation signal from two samples with different antibody targets. (H) Reproducibility of GC methylation signal from two biological replicates of the same antibody target.
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References Unpublished

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