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RNA-GAM captures dynamic changes in 3D genome topology according to cell state

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The interplay between 3D genome architecture and gene expression is dynamic and complex at the single cell level, even within seemingly homogenous populations. Genome architecture is currently well described at varying levels of genomic scale, yet it remains challenging to simultaneously retrieve 3D genome structure and gene expression at the single-cell level to enable the discovery of cause-effect relationships. To facilitate a direct understanding of the relationship between genome-wide DNA conformations of specific cell types and states with gene expression, we have developed RNA-GAM by incorporating a novel RNA detection method into the existing Genome Architecture Mapping (GAM) pipeline. GAM is a ligation-free 3D genomics method built upon statistically determining the co-segregation frequency of genomic loci retrieved from ultrathin cryosections of single cells. With RNA-GAM, we quantify transcript abundance in each subcellular cryosection, in parallel to genomic DNA extraction.
We applied our RNA detection method on a variety of cell types and successfully retrieved sensitive gene expression information which enables identification of cell type and state. Within the GAM pipeline, we use the RNA information extracted from individual cellular slices to stratify sample groups and relate 3D genome structure with gene expression. We applied RNA-GAM to mESCs and currently explore cell-state-specific architectures and their relationship to gene regulation. Specifically, we are investigating changes in genome topology according to gene expression state. Overall, RNA-GAM holds potential to unbiasedly investigate the relationship between chromatin architecture and gene regulation at the genome-wide level in highly heterogeneous cell populations and tissues.

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