Nature Reviews Genetics | Published online 25 January 2016; doi:10.1038/nrg.2016.5

EPIGENOMICS

Parallel single-cell sequencing

A new single-cell analysis method called scM&T-seq comprises the simultaneous genome-wide sequencing of the methylome and the transcriptome from one cell, enabling detailed analyses of how epigenetic heterogeneity relates to gene expression output at each locus.

Multi-parameter sequencing-based analysis of single cells is still in its infancy and has, to date, been limited to probing the transcriptome and genome from the same single cell. Now, researchers extracted and physically separated DNA and RNA, according to a previously established protocol used for parallel genome and transcriptome sequencing (G&T-seq), from 76 individual mouse embryonic stem cells (ES cells) grown in serum and 16 ES cells grown in hypomethylation-inducing media. They then applied single-cell genome-wide bisulfite sequencing (scBS-seq) to the purified DNA and RNA-seq to the RNA to characterize methylomes and transcriptomes from the same single cells.

Comparison of epigenetic heterogeneity in different genomic contexts between 61 serum ES cells obtained using scM&T-seq and 20 serum ES cells sequenced using stand-alone scBS-seq revealed that the two methods yield concordant results. The authors performed a hierarchical clustering analysis of gene-body methylation and gene expression on 300 genes that showed the greatest variance based on DNA methylation. Cell clusters differed when either information source was used alone, indicating that global methylome and transcriptome profiles reveal distinct but complementary aspects of cell state.

"Much of the transcriptional variability we see is thought to be associated with modifications of DNA," explains senior author Wolf Reik (Babraham Institute, Cambridge, UK), "but now we have a technique that allows methylation and transcription heterogeneity to be computationally and mechanistically connected." Single-cell epigenomic techniques have already proven indispensable for studying cellular plasticity and diversity, for example, for stem cells or cancer.

Maximizing the amount of common information on the expression of a locus and its epigenetic state by simultaneously measuring DNA, RNA and epigenetic signatures from the same cell will help to dissect genomic, transcriptional and epigenetic heterogeneity. The future will show whether this technology can fulfil its promise of providing unprecedented insights into how epigenetic mechanisms regulate physiological heterogeneity in health and disease.

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ORIGINAL ARTICLE Angermueller, C. *et al.* Parallel single-cell sequencing links transcriptional and epigenetic heterogeneity. *Nat. Methods* http://dx.doi.org/10.1038/nmeth.3728 (2016)
FURTHER READING Schwartzman, O. & Tanay, A. Single-cell epigenomics: techniques and emerging applications. *Nat. Rev. Genet.* **16**, 716–726 (2015)

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