A landscape of commitment

This issue features epigenetic analysis of cell commitment at many levels in mammalian genomes: during early embryonic development, in stem cells, and in cancer cells. The establishment, propagation and dynamic robustness of cell states is addressed by comprehensive interrogation of the coordination of DNA methylation with the marks and organization of chromatin and programs of gene expression. Understanding this landscape of commitment is essential to interpretation of the functional consequences of genome variation.

Fuchou Tang and colleagues examined paternal and maternal genomes' DNA methylation in gametes and individual cells from preimplantation human embryos using single cell bisulfite sequencing. Demethylation of paternal genomes in zygotes is widespread and more thorough than that of the maternal chromosomes and much of the *de novo* methylation occurs in very local parts of the genome. Cell lineage tracing from early stages can now be achieved using the differential methylation profiles they found.

In a complementary study of the methylome, the transcriptome and the proximity relationships of the 3D genome, Wei Xie and colleagues profiled dissected lineages of early mouse embryos. Noting that global patterns of demethylation and remethylation in early development correlate with chromatin compartments, they conjecture that these correlated events reflect alternative expression states that reinforce distinctions between alternative lineages of embryonic and extraembryonic cells as well as strengthening the identity of adjacent extraembryonic cells and the maternal cells among which they implant.

This balance of demethylation and remethylation activities has a role in the establishment of cell lineages in early embryos. Danwei Huangfu and colleagues deleted the demethylase genes *TET1-TET3* in human embryonic stem cells (ESCs) to demonstrate the role of Tet DNA demethylation activity in protecting uncommitted (bivalently marked) loci from lineage-specific *de novo* methylation. For example, premature hypermethylation of the transcription factor gene *PAX6* impairs access to a neuroectodermal fate. By chromatin immunoprecipitation sequencing these authors were able to correlate sites occupied by Tet1 and *de novo* methylase DNMT3B to the genome-wide methylation patterns, suggesting that this balance is a general feature of lineage establishment. ESC are pluripotent, largely reflecting the cell fate restriction of their origin in the inner cell mass of the embryonic blastocyst stage even when growing in tissue culture. However, they can occasionally give rise to totipotent derivatives. Maria-Elena Torres-Padilla and colleagues quantitated mRNA expressed in single cells of mouse ESC culture to characterize the differences between ESCs and their rare totipotent (2-cell-like) derivatives marked by a MERVL>GFP stage specific marker. They conclude that, like ES cultures, 2-cell-like cells have heterogeneity of expression, implying that both are metastable attractors rather than committed states, and they suggest that it is possible that 2-cell-like derivatives of ES cells do not necessarily adopt the same expression state that embryonic cells transit between their first and third zygotic divisions.

Increasingly, we are realizing that the abnormal cell states of cancer cells can be induced by mutations that produce genome-wide chromatin reprogramming not found in normal cell states. For example, neomorphic *IDH1* mutation in glioma introduces production of 2-hydroxyglutarate, inducing aberrant patterns of DNA methylation and histone methylation. Here, Timothy Chan and colleagues show that *IDH1* engineered immortalized astrocytes and glioma cells in tumor sphere cultures undergo epigenetic changes associated with differential transcription and that some of these changes persist even when the expression of the mutant *IDH1* is withdrawn. How these dysregulated target genes – encoding functions in cell adhesion, cell signaling and transcription factors – bring about cancer cell properties remains to be determined.However, it is interesting that genome destabilization can be activated by endogenous retroelements (ERVs) that become transcriptionally activated loss of silencing marks. Another intriguing consequence of IDH-induced epigenomic deregulation is the emergence of a glioma subpopulation with stem-cell like properties (they express the stem cell marker CD24, increasing their ability to form clones). Finally, parallel derivation and differentiation of multiple lines of induced pluripotent cells (iPSCs) provides a calibration of the experimental variation in these protocols. Against that variation, these cell lines can be used to measure the functional consequences of constitutional genome variation. Investigating the variation in stem cell derived neurons derived from induced pluripotent cells, Jeremy Schwartzentruber and colleagues (News & Views by Gabriel E. Hoffman and Kristen J. Brennand) report about a quarter of the variation in gene expression is introduced during differentiation of iPSC derived neurons, and another quarter depends on donor genome and subsequent reprogramming effects. This study is important in establishing the number of independent genotypes and replicates needed to securely establish the functional variation introduced by donor genome variation. Once we have this information, trait-associated genotypes established by monogenic and genome-wide association studies can be systematically compared in order to demonstrate genetic and complex disease mechanisms in robust cellular models. ❐

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