GENOMICS

Variability in genome structure

Comparisons of genome organization in many individual cells with high-throughput FISH show extensive variation.

Chromosome conformation capture (3C) techniques have become popular tools for studying genomic interactions at different scales, from individual loci with 4C and 5C to the entire genome with Hi-C. Tom Misteli from the National Cancer Institute recalls that from the early days of 3C technologies, he had a fundamental question: “If you see an interaction, does that mean all cells have this interaction, maybe with low affinity, or a few cells have very high-affinity interactions?” Because the data are averaged across millions of cells, this question was difficult to answer.

Elizabeth Finn, a postdoctoral fellow in the Misteli lab, decided to take a closer look at this question and determine just how much structural heterogeneity there is between individual cells. She wanted to know how an interaction found in Hi-C relates to actual physical distance in individual cells. Finn teamed up with the labs of Job Dekker at the University of Massachusetts and Leonid Mirny at MIT, the developers of many 3C methods, and generated high-throughput FISH data for 125 strong interaction pairs identified by Hi-C.

Misteli stresses that their underlying goal was to look at genome structure and that they were agnostic to functional annotation; the interaction pairs they picked for FISH were not driven by known structural elements such as chromatin loops or larger topologically associating domains.

The researchers screened 500 cells for each of the 125 pairs and saw a surprisingly high degree of variability in their spatial distance among cells. While the mean spatial distance of interaction pairs correlated with the interactions seen in Hi-C, the overall distance distribution was variable and continuously pointed to extensive heterogeneity in individual cells. To determine how much of this variability was sequence specific, the researchers shifted the pairs downstream by 500 kb. They saw nearly the same colocalization frequencies and concluded that genomic distance, rather than a particular sequence, is the main contributor to interaction frequency. They also found no evidence for colocalization

of multiple pairs that would indicate higher-order chromatin organization. It is possible that such organization is found in loci not included in this study, but it is unlikely to be general.

While a high degree of structural heterogeneity was obvious, it was not clear from the data whether this spatial variability occurred at the level of the cell or the level of the allele. When she followed the behavior of the two alleles in individual cells, Finn saw little correlation between the localization of the alleles, and concluded that this independent allelic behavior was a driver for overall heterogeneity.

These data raised the interesting question of whether the variability the researchers saw was due to what Misteli calls “dynamic breathing” of the genome or to a fundamentally different structure. “Is there a stable state in which two pieces of DNA are always together or always apart?” he asked.

Their results leave both options open. “Some of the distances we measure between two spots are larger than what you would usually see for dynamic events; this suggests it is not just dynamic.” But Misteli readily adds that more work is needed to resolve this question.

Another question is how such heterogeneous structures can generate stable cell states. Misteli thinks that stability is generated by the averaging of gene activity over time. “Genes show stochastic expression,” he says; “genes blink.” He envisages a model in which a dynamic chromatin structure supports dynamic expression patterns.

One limitation of this work is that it was done in cultured human fibroblasts. “Would you see the same pattern of variability in tissues or an organism?” Misteli asks, and he is keen to focus on this question next.

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Research papers

Finn, E. H. et al. Extensive heterogeneity and intrinsic variation in spatial genome organization. *Cell* **176**, 1502–1515 (2019).

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