METHODS IN BRIEF

CELL BIOLOGY

High-throughput discovery of genome organizers

Mammalian genomes are spatially highly organized, a feature that has a role in many aspects of gene expression and cell biology. The cellular factors involved in regulating and maintaining genome structure have historically been challenging to identify owing to a lack of high-throughput screening methods. To address this issue, Shachar *et al*. developed high-throughput imaging position mapping (HIPMap), in which the location of target genes in the nucleus is monitored using fluorescence *in situ* hybridization (FISH). HIPMap applies fully automated FISH, imaging and data analysis in a 384-well format. The authors used the procedure to screen an siRNA library for factors that led to changes in the positions of the targeted genes. Their screen revealed more than fifty factors involved in genome organization, most of which were not previously identified.

Shachar, S. *et al*. *Cell* **162**, 911–923 (2015).

GENOMICS

Variation in human repeat sequences

Around 5% of the human genome is made up of low-copy repeat regions containing structural and copy-number variations that likely have phenotypic effects, but they are inaccessible to current short-read sequencing technology because the reads cannot be unambiguously aligned. Bishara *et al*. developed an algorithmic solution, the Random Field Aligner (RFA), which at uses the TruSeq synthetic long-read protocol. TruSeq retains contiguity information in long pieces of DNA by fragmenting the genome and barcoding short reads derived from the same long fragment before sequencing pooled reads. RFA uses high coverage of fragments but low coverage of read clouds, groups of reads with the same barcode, to iteratively map the synthetic long reads to a reference. The authors used RFA to discover variants in repeat regions of normal and cancer-derived human genomes.

Bishara, A. *et al*. *Genome Res*. doi:10.1101/gr.191189.115 (18 Aug 2015).

STEM CELLS

Zapping cells improves genome-editing efficiency

Efficient genome-editing tools are needed to correct patient-derived stem cells or model human disease. To engineer targeted changes, scientists have to use editing methods that rely on the generation of double-stranded DNA breaks and their subsequent repair by homologous recombination, which can replace cut DNA with a donor vector sequence but is inefficient. Hatada *et al*. report that low (0.4 Gy) doses of γ-ray or X-ray radiation can increase recombination efficiency in cells by more than 30-fold when used in combination with zinc finger nucleases, transcription activator–like effector nucleases or CRISPR nucleases. The limited exposure to low radiation is safe at the karyotypic and functional levels and may work by 'priming' the repair apparatus of the cell. The authors edited three genomic loci and suggest the potential for high-throughput genome editing.

Hatada, S. *et al*. *Stem Cells Transl. Med.* **4**, 1–13 (2015).

MICROSCOPY

Isotropic super-resolution imaging

Although super-resolution microscopy methods such as photoactivated localization microscopy and direct stochastic optical reconstruction microscopy (dSTORM) can improve lateral resolution by tenfold compared to traditional light microscopy, their axial resolution is still diffraction-limited. To bypass this limitation, Bourg *et al*. developed direct optical nanoscopy with axially localized detection (DONALD). DONALD combines conventional dSTORM with the detection of a fluorescent probe's evanescent light—specifically, its supercritical-angle fluorescence emission. The latter measurement allows for accurate distance measurement between the probe and up to ~150 nm from the coverslip, allowing for an overall isotropic resolution of 20 nm. Using this method, the authors were able to demonstrate isotropic super-resolution imaging of actin and microtubules in mammalian cells.

Bourg, N. *et al*. *Nat. Photonics* **9**, 587–593 (2015).

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