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Single-cell genome sequencing: current state of the science

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Key Points

- Single-cell genome sequencing aims to increase our understanding of complex microbial ecosystems and disease in multicellular organisms by isolating the contributions of distinct cellular populations.
- Acquiring high-quality genotype data after starting from a single molecule of DNA from an individual cell has substantial technical challenges that are continuously being addressed.
- The three main genome amplification methods have differences in their propensity to produce distinct types of artefacts, which should be carefully considered when designing experiments. The experimental design should also

tumour heterogeneity, which have provided new biological insights into tumour formation.

- Single-cell genome sequencing is rapidly evolving, and the use of these techniques is likely to expand as technologies improve and new discoveries are made.

Abstract

The field of single-cell genomics is advancing rapidly and is generating many new insights into complex biological systems, ranging from the diversity of microbial ecosystems to the genomics of human cancer. In this Review, we provide an overview of the current state of the field of single-cell genome sequencing. First, we focus on the technical challenges of making measurements that start from a single molecule of DNA, and then explore how some of these recent methodological advancements have enabled the discovery of unexpected new biology. Areas highlighted include the application of single-cell genomics to interrogate microbial dark matter and to evaluate the pathogenic roles of genetic mosaicism in multicellular organisms, with a focus on cancer. We then attempt to predict advances we expect to see in the next few years.

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Ethics declarations

PowerPoint slide for Fig. 2

PowerPoint slide for Fig. 3

PowerPoint slide for Fig. 4

PowerPoint slide for Fig. 5

PowerPoint slide for Table 1

Glossary

Genetic mosaicism

Occurs when there are at least two genotypes in different cells of the same organism.

Whole-genome amplification

The use of biochemical methods to produce multiple copies of the entire genome.

Optical tweezers

Devices that use a laser to manipulate submicron particles, such as bacterial cells or cellular macromolecules.

Chimaeras

Amplification artefacts formed when two previously disconnected genome

Structural variants

Variation in the genome that occurs as a result of the joining of two previously disconnected genomic locations. A subset of structural variation is copy number variation, which occurs when portions of the genome are amplified or deleted.

Somatic variants

Changes in the genome of an organism that are not present in germ cells and can thus not be passed on to offspring.

Molecular barcoding

Attaching a unique sequence to each molecule as a strategy to more accurately count nucleic acids by correcting for experimental artefacts. This approach is also used to decrease false-positive mutation call rates due to sequencing errors by creating a consensus genotype for each molecule.

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