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Review

Single-Cell Analysis in Cancer Genomics

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Genetic changes and environmental differences result in cellular heterogeneity among cancer cells within the same tumor, thereby complicating treatment outcomes. Recent advances in single-cell technologies have opened new avenues to characterize the intra-tumor cellular heterogeneity, identify rare cell types, measure mutation rates, and, ultimately, guide diagnosis and treatment. In this paper we review the recent single-cell technological and computational advances at the genomic, transcriptomic, and proteomic levels, and discuss their applications in cancer research.

Trends

Recent advances in single-cell technologies have enabled researchers to profile mutations and expression levels of a large number of genes and proteins at individual cells.

Developments of new computational methods have greatly aided the calibration, quantification, and interpretation of single-cell data.

Single-cell analysis has been applied to study cancer initiation, variation, and evolution and will have potentially high clinical impact.

Cancer is a Disease of Multitudes

Cellular heterogeneity, which results from mutation, differences in gene regulation, stochastic variation, or environmental perturbations, is reflected at the genomic, transcriptomic, and proteomic levels. Such heterogeneity is increasingly appreciated as a factor of cancer treatment failure and disease recurrence, because a treatment that targets one tumor cell population may not be effective against another [1]. Not only is cancer itself a complex disease made up of a collection of individually distinct pathologies, but also within each tumor there is significant heterogeneity among different cells. Current theories propose that cancer development involves both a process of clonal evolution from mutated cells of origin and a differentiation hierarchy from cancer stem cells [2]. It is increasingly clear that traditional bulk experiments, which only measure the average profile of the population, have limitations in characterizing complex diseases such as cancer.

Single cells have been studied since the invention of the microscope, but it is not until recently that genome-scale approaches have been applied to single-cell biology [3–7]. For example, microfluidic-based single-cell sorting methods [8,9], high-throughput multiplexed quantitative PCR (qPCR) [10–14] or sequencing approaches [15–23], mass cytometry-based proteomic strategies [24–26], and data analysis methods [27–30] provided an unprecedented opportunity to identify rare cell types, such as cancer stem cells, and to investigate the dynamic processes of cell fate transitions.

One of the important application areas of single-cell analysis is in cancer genomics (Figure 1, Key Figure). Recently, several studies have applied single-cell analysis to characterize the cellular heterogeneity in different cancers [13,23,31–33]. The comprehensive knowledge about cellular heterogeneity will not only provide fundamental insights into development and other biological processes but also have important applications in therapy because drug resistance is often caused by heterogeneous response at the cellular level.

In this paper we review the recent technological and computational advances in single-cell analysis, and discuss their applications in cancer genomics. We conclude by offering a personal view of the potential challenges and future prospects for this field.

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Key Figure

An Overview of Single-Cell Cancer Genomics

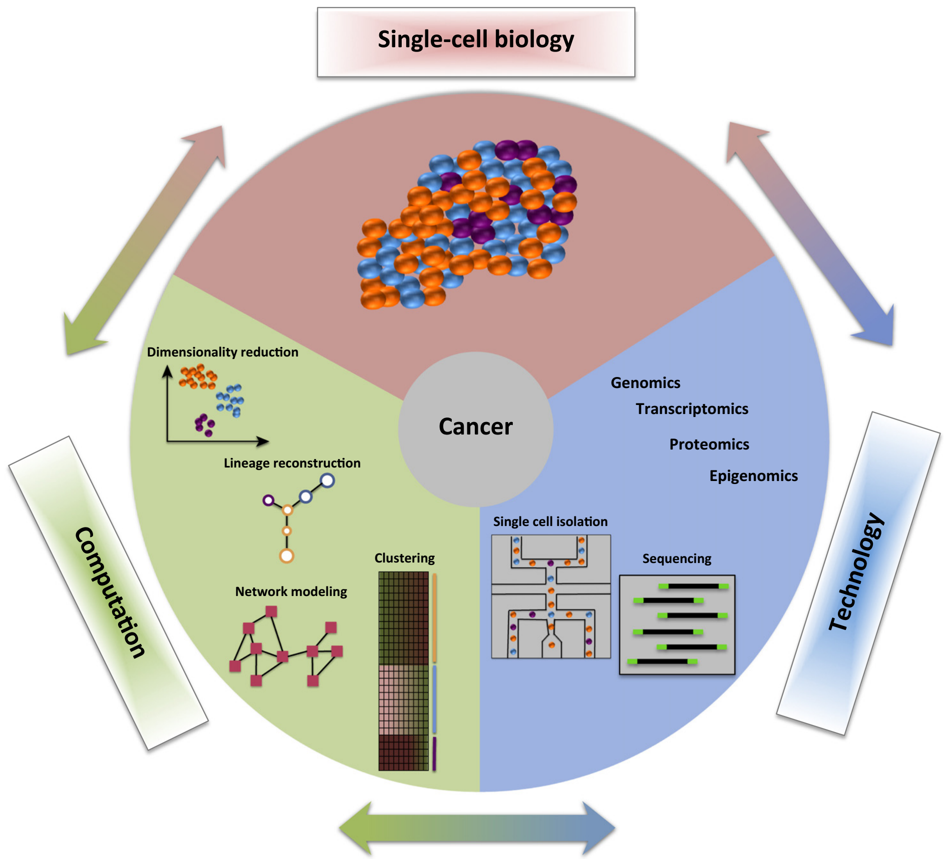

Figure 1. Single-cell technologies are used to generate genomic, transcriptomic, and proteomic data from cancer cells. These data are analyzed by computational methods to identify clusters, lineages, and networks, which in turn generate new biological hypotheses. Biological discoveries in turn guide the development of new technologies and computational approaches. The figure also shows a schematic example with a heterogeneous cancer sample containing three cell types (orange, blue, and purple). An integrated single-cell analysis is used to identify the cell types, lineages, and network profiles.

Technological Developments in Single-Cell Analysis

Methods for single-cell measurement, such as flow cytometry [34], RNA fluorescence *in situ* hybridization (FISH) [35,36], and dynamic profiling of fluorescent fusion proteins [37], were developed years ago and are routinely used in modern labs. However, these traditional methods provide limited information from single-cell samples because only a few genes or proteins can be profiled at the same time. In the past few years a new wave of technologies has emerged in the areas of single-cell isolation, nucleic acid amplification, and genomic/transcriptomic/proteomic profiling (Table 1). These new methods have significantly increased the throughput and scale of single-cell analysis.