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Editorial Letter

Single-Cell Omics in Cancer Research

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Dear Editor-in-Chief,

I wish to share with your readers a technology that is fundamentally transforming biomedical research and rapidly becoming an essential component of investigations. The technology is called single-cell omics, where the term "omics" refers to the study, in totality, of certain biological molecules in a high-throughput manner. In this approach, biological materials, such as DNA molecules (genomics), RNA molecules (transcriptomics), proteins (proteomics), and the complete set of modifications affecting gene expression (epigenomics), are studied in a single cell. Single-cell omics is becoming a valuable tool in cancer research, despite being expensive and requiring complex data manipulations compared to dealing with bulk tumor cells. So why do we have an increasing number of research and clinical trials using single-cell omics platforms? A tumor is a collection of several cell types, including not only the cancer cells but also various other non-cancerous cells such as immune cells, fibroblasts, endothelial cells, pericytes, adipocytes, and other tissue-resident cells. Sequencing of the sample bulk of tumor cells averages their genetic signals and can mask rare but critical populations [1,2]. Analyzing the DNA or RNA, as undertaken in single-cell multiomics, can reveal the identity and the mutational burden of an individual subpopulation, find treatment-resistant cells, and establish how the tumor is changing over time (see Figure 1). This valuable information could not be deciphered when carrying out the standard bulk analysis of the tumour sample. Single-cell genomics can profile the gene expression of every cell in the tumor microenvironment and help understand how they communicate and function [3]. Treatment failure and cancer relapses are often caused by a small subpopulation of therapy-resistant cells that could not be revealed by bulk sequencing, as illustrated in Figure 1. Single-cell profiling could give us a comparison between "before" and "after" relapse and pinpoint the specific cell population behind the relapse. Such knowledge could be crucial for designing combination therapies that are needed to target multiple resistance pathways. The heterogeneity of chronic myeloid leukaemia cells and their impact on therapy response is powerfully illustrated in a recent study by Warfvinge *et al*. using single-cell omics [4].

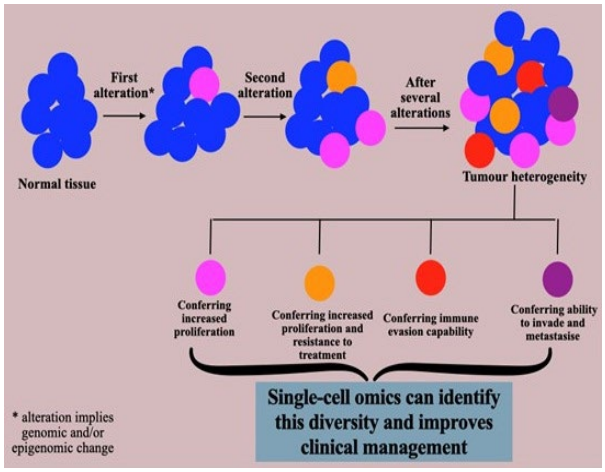

Figure 1: A schematic illustration of how single-cell omics can help identify tumour heterogeneity and aid the management of cancer.

Single-cell expression data and epigenomics have identified a distinct subpopulation of leukemia cells that are resistant to treatment. An outcome that would have remained hidden if traditional "bulk" sequencing had been undertaken. Immunotherapy has been a game-changer in cancer treatment. However, only a subset of patients responds to these therapies, and it's often difficult to predict responders to these treatments. Sequencing of the RNAs in a single cell can be used to monitor how tumour cells and immune cells change over the course of treatment. Additionally, by analyzing the T cell repertoire, a tumour can be predicted to be a good candidate for checkpoint inhibitors if many of the T cells are found to be in a state of "exhaustion." Selecting T cell subtypes that are more effective at killing cancer cells can also improve CAR-T cell therapies. The goal of a successful treatment is to catch cancer early. However, early-stage precancerous lesions are small, heterogeneous, and difficult to detect in bulk specimens, making single-cell omics more suitable for early detection. Moreover,

single-cell omics could be employed in biomarker discovery through the identification of specific cell populations or gene expression signatures that predict prognosis and/or response. An important first step in applying omics technology is the isolation of single cells, for which several advanced strategies have been developed (refer to Figure 2) [5].

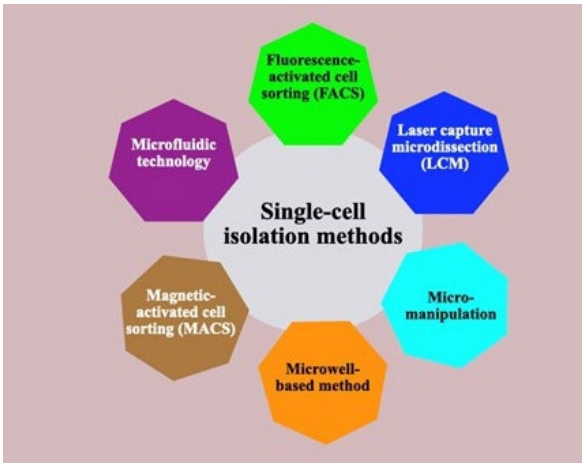

Figure 2: Single-cell isolation methods.

Micromanipulation is one of the simplest procedures involving the manual selection of a single cell under the microscope. Laser capture microdissection (LCM) also separates single cells under the microscope but employs a laser beam to excise specific cells. Fluorescence-activated cell sorting (FACS) represents a substantial advance in cell throughput, targeting cells that are specifically labelled using fluorescent dyes or proteins conjugated to antibodies. Magnetic-activated cell sorting (MACS) offers a simpler and more cost-effective alternative employing magnetic beads conjugated with various ligands, such as antibodies or enzymes, to capture surface proteins on target cells. Microfluidic technology has further advanced single-cell isolation by precisely controlling fluid dynamics within microscale channels. Microwell-based methods are often adopted by commercially available high-throughput technology to deliver the results. Following the cell separation phase, the genetic material from every single cell is converted into a library for sequencing. The data obtained are then subjected to complex computational analysis using bioinformatics to arrive at the results. Although powerful, single-cell omics is still expensive, involving intensive and complex computational work. Despite that, the cost is rapidly going down, particularly when it integrates several omics technologies. Single-cell omics is fundamentally reshaping the landscape of genome analysis and is anticipated to be a future leading edge in precision medicine.

***Keywords*:** Omics; Single cell; Genomic analysis

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