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Review

Recent advances and perspectives on capture and concentration of label-free rare cells for biomedical science and engineering research

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ABSTRACT

Capture and concentration of the rare cells from a heterogeneous population plays an important role in the development of disease diagnostics, therapeutics, and biomedical research/applications. Phenotypic and genetic characterization of these rare cells can provide important information to guide cancer therapy and regenerative medicine. Large-scale supply of the rare cells at high purity and viability is essential, especially on stem cells, cancer stem cells (CSCs), and circulating tumor cells (CTCs). Conventional capture and concentration methods providing efficient and high throughput isolations are introduced; however, most of them require well-defined biochemical markers and immunolabeling procedures which are complicated, uneconomical, and often unreliable. In contrast, the emerging label-free cell capture methods based on biophysical and biomechanical properties of the desired cell population are growing. In this review, we aim to describe the status of label-free rare cell capture and concentration techniques and to highlight exciting new approaches in this field. Label-free rare cell isolation methods using intrinsic biophysical properties such as filtration, size, electrical polarizability, dielectrophoresis, optical dielectrophoresis, and hydrodynamic chromatography are introduced. Moreover, the microfluidic systems adopted to precisely handle cells and interface with other tools have been described earlier; thus, new approaches dealing with merging label-free selection methods and microfluidic systems are merely summarized. Furthermore, the capture and concentration methods using biochemical and materials properties such as cell-materials interaction, spheroid formation, and stem cells/CSCs niche mimicking are highlighted particularly. Advancing cell isolation technique provides the opportunity to avoid the shortcoming of using biochemical labels and presents better flexibility for subsequent characterization, such as on site screening, high throughput screening, and personalized medicine.

1. Introduction of cell isolation

The goal of rare cell capture and concentration is to purify or enrich cell samples into well-defined populations to enhance efficiency in biological and biomedical research and applications, such as cell biology, immunology, stem cell research and cancer stem cell (CSCs) research, allowing for their subsequent analyses of functions and phenotypes. Meanwhile, the growing interest in personalized medicine, in which treatments are tailored to the prognoses of patients, is further driving the need for rare cell isolation. Identification and isolation can be achieved using specific biological markers such as antibodies or by taking advantage of differential mechanical, electrical, or niche properties between subpopulations of the cells using label-free strategies. As shown in Fig. 1, density gradient centrifugation, fluorescence-activated cell sorting (FACS), and magnet-activated cell sorting (MACS) are

Abbreviations: ABC transporter, adenosine triphosphate-binding cassette transporter; BCRP, breast cancer resistance protein; CKs, cytokeratins; CSCs, cancer stem cells; CTCs, circulating tumor cells; DEP, dielectrophoresis; EpCAM, epithelial cell adhesion molecule; EMT, epithelial-mesenchymal transition; HCC, hepatocellular carcinoma; hESCs, human embryonic stem cells; HSCs, Hematopoietic stem cells; MSCs, mesenchymal stem cells; FACS, fluorescence-activated cell sorting; MACS, magnet-activated cell sorting; SP, side population; FFF, field-flow fractionation; ODEP, optically-induced dielectrophoresis; PAH, poly(allylamine hydrochloride); PSS, poly(sodium-4-styrene-sulfonate); HA, hyaluronic acid; PDMS, polydimethylsiloxane; PEM, polyelectrolyte multilayer; QCM-D, quartz crystal microbalance with dissipation monitoring; SLB, supported lipid bilayer; TCPS, tissue culture polystyrene.

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Table 1
Conventional label-based isolation methods and markers.

Cell type		Method	Markers	Sources
Stem cells	Skeletal stem cells	FACS	CD45	[47]
	Mesenchymal stem cells	FACS	CD271, CD146, CD49f, CD349, CD200, CD105, CD73, CD90, CD271	[8]
	Clonogenic human central nervous system stem cells	FACS	CD133, CD34- CD45-	[48]
	Hematopoietic stem cells	SP	Hoechst 33342	[9]
CSCs	Glioblastoma	FACS	CD133	[49]
	Breast cancer cells	FACS	ALDH, CD133, CD176, CD56, CD16, CD44, CD24	[50,51]
	Prostate cancer cells	FACS	CD44, CD133	[50]
	Liver cancer cells	FACS	CD133, CD44, CD90, CD13, EpCAM	[50]
	Colon cancer cells	FACS	CD44, CD133, CD24, CD166	[50,52]
	Breast cancer cells	MACS	CD44, CD24	[53]
	Breast, HCC, lung, head, neck, and glioblastoma	SP	Hoechst 33342	[32–37]
CTCs	Breast cancer cells	FACS	EpCAM	[54]
	Gastric cancer cells	FACS	EpCAM, CD44	[55]
	Gastric cancer cells	MACS	EpCAM, CK8, CK18, CK19, CD45	[56]

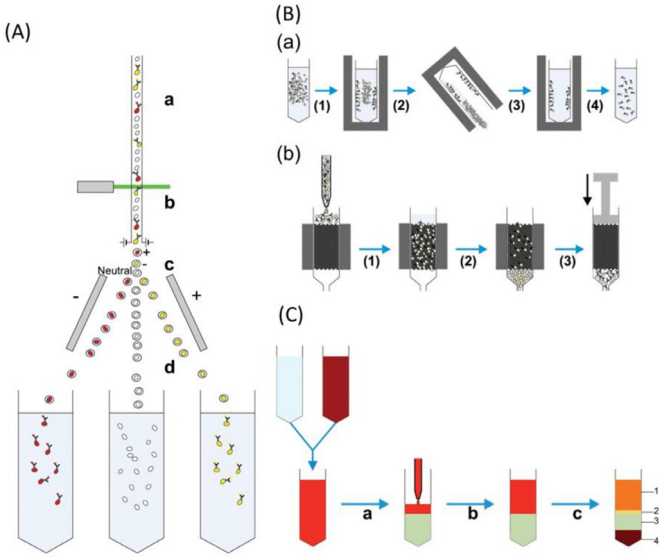

Fig. 1. Conventional cell isolating. (A) Cell sorting by FACS. (B) Common methods used for magnetic cell separation. (a) Tube-based separation. (b) Column-based separation. (C) Whole blood cell separation by density gradient centrifugation. (Reprinted from [1], with permission from SAGE Publications Ltd.).

conventional cell isolation methods that are commercially available and widely used [1]. These methods can sort and enrich desired cell populations or deplete some specific cell populations. Indeed, antibody-labeled based approaches are often associated with high efficiencies which made FACS the mainstays of modern cell sorting technologies. However, these methods need to use immunologic strategies to label cells which affect subsequent characterization and culture. Therefore, techniques that are more efficient, simplified, and can be broadly applied on the collection and enrichment of stem cells, CSCs, and circulating tumor cells (CTCs) are highly desired.

2. Antibody-labeled based cell isolation of stem cells, CSCs, and CTCs

Cell isolation techniques can be classified into two categories. The first category is the techniques based on affinity (chemical, electrical, or magnetic couplings), and the second category is those based on physical parameters (size/density, electrical polarizability, or optical properties). Table 1 lists the conventional label-based isolation methods and the immunological labeling markers used on the sorting and identification of different types of stem cells, CSCs, and CTCs.

2.1. Label-based cell isolation methods

There is a strong incentive to purify, enrich, maintain, and facilitate production of a large quantity of stem cells for a wide variety of biological and medical applications. Previously, some methods including selective culturing, flow cytometric sorting, and magnetic-activated cell sorting have been applied as the first step to isolate the stem cells from primary cells, as listed in Table 1 [2–5]. Mesenchymal stem cells (MSCs) were first isolated and identified from bone marrow as fibroblastic colony-forming units. Previous review has sorted out the markers which have been used to identify MSCs, including high expression of CD105, CD73, CD90, CD271 and lack expression of CD45, CD34, CD14, and CD19 [6,7]. Besides bone marrow, MSCs have been isolated from adipose tissue, placenta, dental pulp, synovial membrane, peripheral blood, umbilical cord, and umbilical cord blood [8]. However, there is no consensus on a single surface marker to identify MSCs from different sources currently. Also, the stem cells in clonogenic human central nervous system have been sorted using the antibodies combining $CD133^+$, $CD34^-$, and $CD45^-$ from fetal brain tissue [9]. These affinity-based methods require well-defined biomarkers to isolate scarce stem cells from the entire population and therefore are unusable when a target cell lacks effective biomarkers.

CSCs are a sub-population of cancer cells within tumors with capabilities of self-renewal, differentiation, and tumorigenicity when are transplanted into an animal host. Preclinical studies have demonstrated that CSCs mediate tumor metastasis and resistance to radiation or conventional chemotherapy [10–12]. Therefore, the discovery of CSCs in solid tumors has changed our view on carcinogenesis and provided a new insight on therapeutic targets on cancer treatment. Technical advancements in stem cell technologies such as cell isolation using FACS, MACS, and transplantation into immunodeficient mice facilitate the identification of CSCs in solid tumors. CSCs are often characterized by elevated expression of some of stem cell markers [11]. As listed in Table 1, a number of cell surface markers such as CD44, CD24, and CD133 are generally used to identify and enrich CSCs and also sort by FACS or MACS [13,14]. In addition, Hoechst low side population (SP) cell sorting, chemo-, and radio-therapeutic drug selection were widely used as conventional isolation methods [15–17].

Most CSCs assays have so far depended on the use of a variety of different cell surface markers to isolate CSCs using FACS, especially CD133 [18,19]. Previous studies have revealed that $CD133^+$ cells can form tumors in severe combined immunodeficiency mice. In addition, $CD133^+$ population of huh7 cells and $CD133^+$

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