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Recent insights into the development of nanotechnology to detect circulating tumor cells

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ABSTRACT

Circulating tumor cells (CTCs) produced from primary tumors act as seeds for metastasis, leading to the majority of cancer-related deaths. Currently, in cancer research, these cells have attracted much attention in studying the process of metastasis. Various studies in the past decade have enlightened the role of CTCs as potential biomarkers in cancer diagnosis and prognosis. As a result, the analysis of CTCs could act as a substitute for characterizing the nature of primary tumors and provide unique insights into the metastatic process. The detection of CTCs in the blood samples of a cancer patient is technically challenging because of the extremely low abundance of CTCs among a large number of other blood cells. Therefore, novel methods for the detection of CTCs are highly recommended. In this feature article, we discuss the recent progress in nanotechnology for the detection of CTCs along with perspectives on future opportunities.

Contents

1. Introduction

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. It is a leading cause of death and the burden is expected to grow worldwide with population growth and aging, mainly in developing countries, in which about 82% of the world's population resides [1]. By 2030, the global burden is expected to grow to 21.7 million new cancer cases and 13 million cancer deaths simply due to the growth and aging of the population [2]. Generally, metastasis is considered as the most important clinical indicator of cancer and 90% of deaths associated with cancer are directly attributable to metastasis [3,4]. The metastatic process is a complex series of events in which malignant cells from the primary tumor first invade the basement membrane, subsequently migrating into the circulation either directly via a blood vessel or indirectly via a lymphatic vessel to finally spread to distant sites (Fig. 1) to form metastasis [5,6]. Therefore, the capture of rare cells from a peripheral blood has the potential to advance our understanding and treatment of different cancers. Circulating tumor cells (CTCs) are one example of a rare cell that shed into the circulatory system from the primary tumor and is the basis for the later development of metastasis [7–9]. CTCs are widely considered as an important factor in the metastatic process. They are malignant cells that migrate from primary cancer tissues into the bloodstream to develop metastasis [10–12]. Even though CTCs are very rare in whole blood, they have been found in patients with almost all types of cancer such as colon, liver, lung, pancreatic, and prostate cancer. It is evident that even in patients with advanced diseases, CTCs exist in extreme rarity in blood, and there are significant technical challenges in their isolation and the use of CTCs as a real-time liquid biopsy has received major attraction over the past years [5,10–16]. Therefore, the isolation of these rare CTCs from the billions of blood

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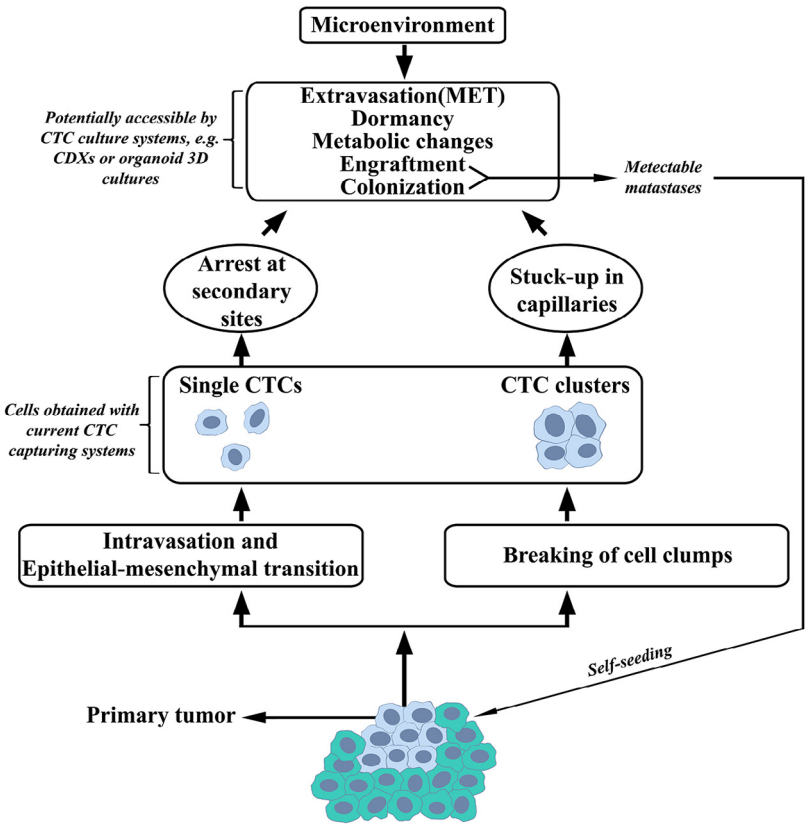

Fig. 1. Schematic representation of metastasis.

cells has been a challenge until recent times. As CTCs are rare in the peripheral blood, and as they are heterogeneous and aggregative, their isolation has become a major impediment. Consequently, the detection and analysis of CTCs from patients with metastatic malignancies have become active areas of research [17–22]. At present, nanotechnology has been making a considerable impact on cancer diagnosis and therapeutic management in revolutionary ways, particularly; in the development of nanoscale devices for simultaneous detection and treatment of CTCs [23]. This review will cover recent insights into the development of nanotechnology to detect CTCs for effective cancer management.

2. Isolation and characterization of circulating tumor cells

Liquid biopsies are noninvasive examinations using blood or fluids that can detect CTCs or the products of tumors that are shed into biological fluids from primary or metastatic tumors [23]. Therefore, the isolation and characterization of CTCs are very important in elucidating the process of cancer metastasis and in clinical decision-making. Isolation must be repeatable, reliable, rapid, cost-effective, capable of processing clinically relevant volumes of blood, and compatible with process automation and downstream CTC analysis [24]. CellSearch system (Janssen Diagnostics) is the only existing approach approved by the US Food and Drug Administration (FDA) for CTC isolation and enumeration. Other means of CTC isolation are available, but they are mostly restricted to the bench with limited capacity to process large blood volumes. Harouaka et al. [24] and Friedlander et al. [17] summarized the methods of CTC isolation and molecular characterization in their reviews. Cancer patients may have only up to approximately hundreds of CTCs per milliliter of blood, whereas common blood cells exist at more than 10^9 cells/mL [18]. Therefore, the presence of CTCs is insignificant by hematopoietic cells [25]. The size of CTCs is generally larger than that of normal blood cells and there is a significant overlap in size of CTCs and that of leukocytes, which might hinder size-based separation processes. The diameter of CTCs is three to four times as large as the bores of capillaries in distant organs [26,27]. High CTC numbers correlate with aggressive diseases, increased metastasis, and decreased time to relapse [27]. CTCs are heterogeneous in nature and there is clear discrepancy in the gene expression between primary tumors and CTCs as well as heterogeneity within the population [28,29]. Because of this nature, it is possible to identify the origin tissue of CTCs by expression profiling studies to detect organ-specific metastatic signatures. CTC isolation involves numerous factors including cell elasticity, cell type, density and quantity of adhesive elements, immunoaffinity interactions, substrate material, surface topography, channel dimensions, and flow conditions. Acoustophoresis is a recent method developed for label-free separation and sorting of CTCs from whole blood. During this process, the force of acoustic waves moves larger cells, such as CTCs and white blood cells (WBCs), to the center of the separation channel, leaving red blood cells and other small particles at the outer edges of the channel [30,31]. Recently, by utilizing novel fabrication techniques, various nanostructured substrates have emerged as ultrasensitive platforms for CTC isolation [32–34]. With the combination of cell release techniques and nanostructured substrates, one can expect tremendous enhancements in cell capture and release. Early detection and treatment of metastatic spread is crucial for disease outcome, and CTCs offer the ability to target metastasis in real time. However, the diversity of published assays using different principles to enrich and identify CTCs has puzzled the cancer research community. Therefore, constructive research is still required to trigger advances in the isolation, characterization, and understanding of the biology of CTCs and to apply laboratory findings to clinical settings.