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Review

Clinical and biological significance of circulating tumor cells in cancer

Takaaki Masuda, Naoki Hayashi, Tomohiro Iguchi, Shuhei Ito, Hidetoshi Eguchi, Koshi Mimori*

Kyushu University Beppu Hospital, Department of Surgery, Japan

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ABSTRACT

During the process of metastasis, which is the leading cause of cancer-related death, cancer cells dissociate from primary tumors, migrate to distal sites, and finally colonize, eventually leading to the formation of metastatic tumors. The migrating tumor cells in circulation, e.g., those found in peripheral blood (PB) or bone marrow (BM), are called circulating tumor cells (CTCs). CTCs in the BM are generally called disseminated tumor cells (DTCs). Many studies have reported the detection and characterization of CTCs to facilitate early diagnosis of relapse or metastasis and improve early detection and appropriate treatment decisions. Initially, epithelial markers, such as EpCAM and cytokeratins (CKs), identified using immunocytochemistry or reverse transcription polymerase chain reaction (RT-PCR) were used to identify CTCs in PB or BM. Recently, however, other markers such as human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and immuno-checkpoint genes also have been examined to facilitate detection of CTCs with metastatic potential. Moreover, the epithelial-to-mesenchymal transition (EMT) and cancer stem cells (CSCs) have also received increasing attention as important CTC markers owing to their roles in the biological progression of metastasis. In addition to these markers, researchers have attempted to develop detection or capture techniques for CTCs. Notably, however, the establishment of metastasis requires cancer-host interactions. Markers from host cells, such as macrophages, mesenchymal stem cells, and bone marrow-derived cells, which constitute the premetastatic niche, may become novel biomarkers for predicting relapse or metastasis or monitoring the effects of treatment. Biological studies of CTCs are still emerging. However, recent technical innovations, such as next-generation sequencing, are being used more commonly and could help to clarify the mechanism of metastasis. Additionally, biological findings are gradually being accumulated, adding to our body of knowledge on CTCs. In this review, we will summarize recent approaches to detect or capture CTCs. Moreover, we will introduce recent studies of the clinical and biological importance of CTCs and host cells.

* *Corresponding author*. Department of Surgery, Kyushu University Beppu Hospital, 4546 Tsurumihara, Beppu 874-0838, Japan. Tel.: +81 977 27 1645; fax: +81 977 27 1651.
E-mail address: kmimori@beppu.kyushu-u.ac.jp (K. Mimori).
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1. Introduction

In the field of cancer research, liquid biopsy has attracted much attention as a new screening or monitoring tool for patients with cancer. Liquid biopsies are noninvasive tests using blood or fluids that can detect circulating tumor cells (CTCs) or the products of tumors, such as fragments of nucleotides or proteins that are shed into biological fluids from primary or metastatic tumors. Such biopsies are expected to be informative or easily accessible tools to provide comprehensive information regarding cancers beyond conventional biopsies. Moreover, these biopsies may enable us to collect information reflecting different phases of the metastatic process and may help clinicians to achieve early diagnosis of malignancies or accurately predict metastasis or recurrence. This methodology has developed gradually since it was first proposed by Mandel and Metais (1948) around 70 years ago because the accuracy of diagnosis must be at least as good as that of conventional biopsy.

There are 3 materials that may be detected in liquid biopsy: CTCs, cell-free DNA (cfDNA), and exosomes (Figure 1). CTCs are circulating cancer cells that are shed into vessels from tumors and have the potential to develop metastatic lesions. cfDNA is short, fragmented DNA released from cancer cells after apoptosis or necrosis (Bettegowda et al., 2014; Schwarzenbach et al., 2011). The study of cfDNA is an active area of cancer research because cfDNA can provide large amounts of information regarding the patient's cancer and can be analyzed comprehensively using next-generation sequencing. Finally, exosomes, a hot topic in the field of intercellular communication, are small membrane-enveloped vesicles containing functional biomolecules (i.e., protein, RNA, and DNA) that can be transferred to recipient cells (Raposo and Stoorvogel, 2013). Tumor-derived exosomes are thought to function to prepare a favorable microenvironment at future sites of metastasis (called the premetastatic niche) (Hoshino et al., 2015). Moreover, exosomes are expected to be useful biomarkers because they are remarkably stable in fluids.

Currently, CTCs have some advantages over cfDNA and exosomes in clinical applications. For example, CTCs can be identified morphologically, and molecular characterization of CTCs can be performed using a variety of modalities (Ilie et al., 2014). It is possible to detect cancer cells by virtue of DNA alterations, such as somatic mutations and copy number aberrations, using cfDNA or exosomes. However, these methods are technically difficult and expensive owing to the low amounts of these materials in circulation. Furthermore, the biological signatures of CTCs, such as the epithelial-to-mesenchymal transition (EMT) or cancer stemness, which are thought to dictate tumorigenic or metastatic phenotype and resistance to therapies in circulating systems, can be useful in clinical and diagnostic applications. Thus, CTCs have the potential to provide large amounts of biological information.

In this review, we will focus on CTCs in the peripheral blood (PB) or bone marrow (BM), which have been well studied and are currently being used in the clinical setting. Additionally, we will discuss detection methods and the clinical and biological significance of CTCs in cancer.

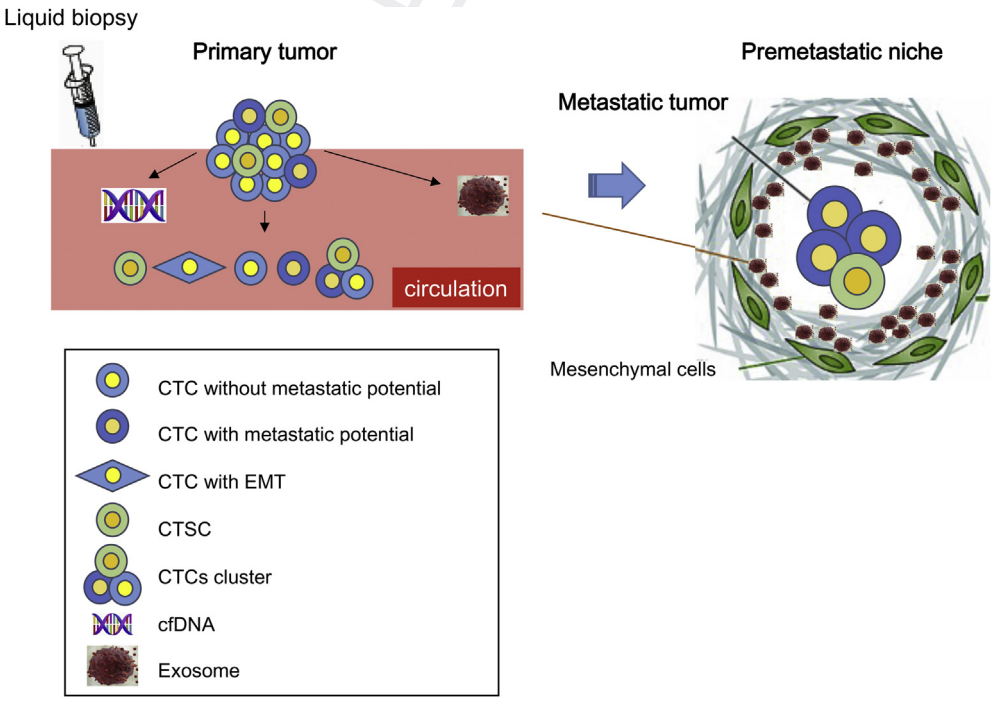

Figure 1 – Circulating biomarkers in tumor metastasis. Cancer cells dissociate from primary tumors, migrate to distal sites, and finally colonize at the premetastatic niche, where mesenchymal cells facilitate metastasis by communication between cancer cells and mesenchymal cells using intercellular messengers, such as exosomes.

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