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Review

Cultured circulating tumor cells and their derived xenografts for personalized oncology

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Abstract Recent cancer research has demonstrated the existence of circulating tumor cells (CTCs) in cancer patient's blood. Once identified, CTC biomarkers will be invaluable tools for clinical diagnosis, prognosis and treatment. In this review, we propose *ex vivo* culture as a rational strategy for large scale amplification of the limited numbers of CTCs from a patient sample, to derive enough CTCs for accurate and reproducible characterization of the biophysical, biochemical, gene expressional and behavioral properties of the harvested cells. Because

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of tumor cell heterogeneity, it is important to amplify all the CTCs in a blood sample for a comprehensive understanding of their role in cancer metastasis. By analyzing critical steps and technical issues in *ex vivo* CTC culture, we developed a cost-effective and reproducible protocol directly culturing whole peripheral blood mononuclear cells, relying on an assumed survival advantage in CTCs and CTC-like cells over the normal cells to amplify this specified cluster of cancer cells.
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1. Introduction

Given its life-threatening consequences, cancer metastasis could be considered the most crucial topic in cancer research. The mechanism of metastasis should be intensely investigated to define the critical players for therapeutic targeting to improve patient survival. Based on historical precedents, in which once-incurable diseases became curable or successfully managed by medical oncologists after advances in biomedical and clinical science [1,2], cancer metastasis will be curable in the future. The overall cancer death rate in the United State, for example, has been falling over the last few decades [3], thanks mainly to the identification of tobacco use as an oncogenic risk factor and a protracted period involving in multistep nature of carcinogenesis. In addition, the recognition of extensive tumor cell heterogeneity has led to personalized oncology, which is markedly improving cancer treatment and patient survival [4—6]. A full understanding of metastatic tumor pathophysiology, in combination with a careful examination of the tumor microenvironment for a clear definition of participant cell types and the signaling network in cancer-stromal and cancer-host immune interaction, may provide clinicians with critical mechanistic insights into the treatment of cancer metastasis [7,8].

This review discusses one of our ongoing research projects focusing on isolation and characterization of circulating tumor cells (CTCs) following *ex vivo* culture. Expanding CTCs in large quantities will facilitate detailed genotypical and phenotypical examination, allowing causal abnormalities driving cancer metastasis to be accurately identified and exploited as biomarkers for cancer diagnosis, prognosis and treatment. Thus, establishment of a highly reproducible and efficient CTC propagation protocol holds the promise for advancing precision medicine and personalized oncology. This review summarizes the current status of high quality CTC research results with special emphasis on *ex vivo* culture of this specific cancer cell type. Based on published literature and our own work, we comment on critical issues facing the development of CTC culture methodologies and propose a rational strategy for culturing CTCs from cancer patient peripheral blood samples. The goal of this discussion is to attract research interest to the development of a cost-effective and reproducible protocol for *ex vivo* culture of a limited number of CTCs from a given clinical blood sample into a large population amendable to molecular characterization.

2. Limitations in the research of cancer metastasis

Many confounding factors make the study of cancer metastasis more difficult than the study of oncogenic initiation, promotion and progression. Firstly, the study of cancer initiation is based on a unified hypothesis, which postulates that cancer initiation is due to genomic mutation or genetic abnormality, while environmental risk factors promote these perturbations and culminate in cancer development and local invasion. In contrast, metastasis is shown to be the result of interplay between cancer cells and resident cells of the tumor microenvironment, involving mesenchymal, endothelial and immune cells at secondary organ sites [9—11], where many of these bystander cell types potentially affect cancer cells through multiple reciprocity [12,13]. The presence of plural variants both in heterogeneous cancer cells and host microenvironment makes identification of critical effectors difficult. Secondly, the study of cancer development has a longer history facilitated by having immortalized cell lines as study subjects and genetically reconstituted animal models to investigate how specific genetic mutations affect cancer development. The study of cancer metastasis is less granular, due to the difficulty of manipulating the drivers of cancer metastasis, while animal models often fail to recapitulate human metastatic profiles. Thirdly, cancer initiation and development can be studied with defined experimental systems, in which the effect of a suspected causal factor can be quantitatively evaluated by multiple modalities such as cell proliferation, apoptosis, migration, invasion and xenograft tumor formation. The study of cancer metastasis, by contrast, is often hindered by a lack of optimal model systems to decipher the interaction between cancer cells and the tumor microenvironment at the metastatic site. Finally, from the therapeutic perspective, many primary cancers can be cured either by surgery and/or adjuvant therapy, while there is a general lack of confidence in the curability of cancer metastasis [14—16], which often leads to the patient's demise. It is challenging for investigators to establish reliable *in vitro* models to delineate the mechanism of cancer metastasis at an organismic level. It would be ideal if metastatic cancer cell lines could be established routinely from each individual cancer patient.

Human cancers are broadly categorized into two groups according to their lineage origin, tumors from mesenchymal lineage and cancers of epithelial cell origin. Though the

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