Visualized Cancer Medicine 2024, **5**, 10

https://doi.org/10.1051/vcm/2024012

Available online at:
https://vcm.edpsciences.org

VIEWPOINT OPEN ACCESS

Detection and characterization of circulating tumor cells and pre-metastatic cancer cells: Questions 108–109 in the 150 most important questions in cancer research and clinical oncology series

Xin Hong[1,2,3,*], and Wenyong Zhang[2,4,*]

[1] Department of Biochemistry, School of Medicine, Southern University of Science and Technology, Shenzhen, 518055, Guangdong, China
[2] Key University Laboratory of Metabolism and Health of Guangdong, Southern University of Science and Technology, Shenzhen, 518055, Guangdong, China
[3] Guangdong Provincial Key Laboratory of Cell Microenvironment and Disease Research, Southern University of Science and Technology, Shenzhen, 518055, Guangdong, China
[4] Department of Pathology, School of Medicine, Southern University of Science and Technology, Shenzhen, 518055, Guangdong, China

Received 18 July 2024, Accepted 23 November 2024, Published online 3 January 2025

Abstract – In this article, the authors raise two key questions: 108. Can we develop automated noninvasive detection coupled with single-cell omics technologies that can simultaneously identify and characterize the biological properties of circulating tumor cells using peripheral blood samples from cancer patients? 109. Can we identify cancer cells with metastatic potential in the primary tumor even before metastatic progression for more precise targeted therapies that prevent the spreading of cancer cells? The background introduction and the application potentials of answering these questions are included.

Key words: Circulating tumor cells (CTCs), Noninvasive detection, Single-cell omics, Pre-metastatic tumor cells, Functional imaging.

108. Can we develop automated noninvasive detection coupled with single-cell omic technologies that can simultaneously identify and characterize the biological properties of circulating tumor cells (CTCs) using peripheral blood samples from cancer patients?

While traditional biopsy methods are invasive and risky, especially for patients with advanced cancer, noninvasive analysis through peripheral blood samples (liquid biopsy) offers significant clinical advantages [1, 2]. As an important component of liquid biopsy, circulating tumor cells (CTCs) are considered metastatic precursors that give rise to distant metastases. The analysis of individual CTCs from blood samples provides real-time tracking of cancer evolution and dynamic response to distinct therapeutic courses. The technological revolution of single-cell omic technologies allows for the comprehensive characterization of CTCs with unprecedented resolution.

Recent studies have underscored the importance of CTC clusters as key players in cancer progression, highlighting their increased malignancy and metastatic potential when compared to single CTCs. It has been reported that the metastatic potential of CTC clusters is 23–50 times greater than that of single CTCs in breast cancer [3]. Homotypic clustering of CTCs can be formed by the expression of multiple adhesion and junction proteins such as CD44 and plakoglobin. They often display altered behavior like increased stem stemness, decreased anoikis, and enhanced proliferation [4]. Heterotypic CTC clusters are formed when CTCs integrate with other cell types within the blood circulation, which can bypass certain immune surveillance and exhibit greater resistance to shear stress, promoting their escape from the primary tumor and establishment in distant tissues [5]. By analyzing the genetic, transcriptomic, proteomic, and epigenetic profiles of single CTCs and CTC clusters, researchers can uncover the heterogeneity within a tumor that is often masked in the analyses of bulk tumor tissues. Such comprehensive profiling strategies may reveal specific mutations, gene expression patterns, and other molecular characteristics unique to each single CTC or CTC cluster, providing key biological insights into the mechanisms of metastatic progression and identifying novel therapeutic strategies for anti-metastasis treatment [6, 7].

*Corresponding authors: hongx@sustech.edu.cn; zhangwy@sustech.edu.cn

Manual detection and analysis of CTCs are time-consuming and prone to error, whereas the advancement of microfluidic engineering and automation technologies ensures high-throughput, consistent, and accurate processing of CTC samples [8]. Microfluidic systems are also capable in isolation and characterization of CTC clusters based on size or biomarker, facilitating patient-derived cell line establishment, which provide a fundamental model to study metastasis [9]. Furthermore, integrating advanced computational tools, such as deep learning and artificial intelligence, may enhance the ability to characterize CTCs with ultra-high sensitivity and specificity.

Therefore, the development of automated noninvasive detection coupled with single-cell omic technologies for CTC analysis holds great promise for improving cancer detection, treatment, and real-time monitoring of therapeutic outcomes.

109. Can we identify cancer cells with metastatic potential in the primary tumor even before metastatic progression for more precise targeted therapies that prevent the spreading of cancer cells?

Metastasis is the leading cause of cancer-related deaths, responsible for about 90% of fatalities. Identifying cells with metastatic potential in the early stage of cancer development may hold the key for improving patient outcomes. However, the major challenge of cancer treatment is the inherent tumor heterogeneity, with diverse cell populations exhibiting varying degrees of aggressiveness and metastatic potential. Understanding the specific biological properties of cells poised to metastasize – such as particular genetic mutations, gene expression profiles, and signaling pathways may allow us to develop more precise and effective targeted therapies against the potential metastatic drivers [10, 11].

Early identification and comprehensive characterization of cancer cell subpopualtions with metastatic potential would allow for better patient stratification and personalized treatment. Patients identified with high-risk metastatic clones can be monitored more closely and treated more aggressively, while those without these cells can avoid overtreatment. Such stratification is extremely important for resource allocation in the clinic and reduces the physical, psychological, and financial burden on patients. Furthermore, the investigation of molecular mechanisms driving metastatic transition within each primary tumor can uncover novel therapeutic candidates that may effectively block metastasis at the early stage of cancer progression [12].

Functional imaging technologies are playing an increasingly important role in characterizing systemic metastases. This powerful approach allows non-invasive monitoring of cancer progression and therapeutic efficacy, offering a more effective strategy to cancer diagnosis and treatment [13]. The novel molecular imaging techniques go beyond traditional anatomical imaging by providing dynamic information, such as receptor expression, metabolic activity, and cellular response to targeted therapy. Hyperspectral imaging (HSI) mingles the power of imaging and spectroscopy to obtain both spectral and spatial information [14]. Hyperspectral imaging has demonstrated promise in detecting early-stage tumor and micrometastases, monitoring microenvironment changes, and assessing tumor margin without molecular labeling. However, the sensitivity of these imaging technologies is often insufficient to detect the rare and small populations of highly metastatic cancer cells with great heterogeneity, especially in the case of CTCs [15]. Due to the limit of tissue penetration depth, imaging technologies struggle to capture the full spectrum of changes that indicate high metastatic potential subpopulations. It is also urgent to develop advanced algorithms and establish spectral databases to help in interpreting the complex hyperspectral data.

In summary, the identification and characterization of cancer subpopulations with metastatic potential in the primary tumor is pivotal for advancing cancer treatment. It may open the avenue for early intervention, precise patient stratification, and the implementation of personalized cancer therapies.

Funding

This research was funded by the National Natural Science Foundation of China (NSFC) fundings: 82173391, T2250610233; Guangdong provincial funding awards: 2021QN02Y112, 2023A1515010287.

Conflicts of interest

The authors declare no competing financial interests.

Data availability statement

Data availability is not applicable to this article.

Author contribution statement

X.H. and W.Z. conceived, designed, wrote and reviewed the study.

Ethics approval

Ethics approval is not applicable to this article.

Informed consent

Informed consent is not applicable to this article.

References

1. Alix-Panabieres C, Pantel K. Liquid biopsy: from discovery to clinical application. Cancer Discov. 2021;11(4):858–873.
2. Haber DA, Velculescu VE. Blood-based analyses of cancer: circulating tumor cells and circulating tumor DNA. Cancer Discov. 2014;4(6):650–661.
3. Aceto N, Bardia A, Miyamoto DT, et al. Circulating tumor cell clusters are oligoclonal precursors of breast cancer metastasis. Cell. 2014;158(5):1110–1122.
4. Yufan Y, Guanyin H, Jingru L, et al. Circulating tumour cell clusters: isolation, biological significance and therapeutic implications. BMJ Oncology. 2024;3(1):e000437.
5. Schuster E, Taftaf R, Reduzzi C, et al. Better together: circulating tumor cell clustering in metastatic cancer. Trends Cancer. 2021;7(11):1020–1032.
6. Keller L, Pantel K. Unravelling tumour heterogeneity by single-cell profiling of circulating tumour cells, Nat Rev Cancer. 2019;19(10):553–567.
7. Liu J, Lian J, Chen Y, et al. Circulating tumor cells (CTCs): a unique model of cancer metastases and non-invasive biomarkers of therapeutic response. Front Genet. 2021;12:734595.

8. Banko P, Lee SY, Nagygyorgy V, et al. Technologies for circulating tumor cell separation from whole blood. J Hematol Oncol. 2019;12(1):48.
9. Macaraniag C, Luan Q, Zhou J, et al. Microfluidic techniques for isolation, formation, and characterization of circulating tumor cells and clusters. APL Bioeng. 2022;6(3):031501.
10. Ganesh K, Massague J. Targeting metastatic cancer. Nat Med. 2021;27(1):34–44.
11. Klein CA. Cancer progression and the invisible phase of metastatic colonization. Nat Rev Cancer. 2020;20(11):681–694.
12. Liu Y, Cao X. Characteristics and significance of the pre-metastatic Niche. Cancer Cell. 2016;30(5):668–681.
13. Bai JW, Qiu SQ, Zhang GJ. Molecular and functional imaging in cancer-targeted therapy: current applications and future directions. Signal Transduct Target Ther. 2023;8(1):89.
14. Zhang Y, Wu X, He L, et al. Applications of hyperspectral imaging in the detection and diagnosis of solid tumors. Transl Cancer Res. 2020;9(2):1265–1277.
15. Winnard PT Jr., Pathak AP, Dhara S, et al. Molecular imaging of metastatic potential. J Nucl Med. 2008;49(Suppl 2):96S–112S.

Cite this article as: Hong X & Zhang W. Circulating tumor cells and identifying pro-metastatic cancer cells: Questions 108–109 in the 150 most important questions in cancer research and clinical oncology series. Visualized Cancer Medicine. 2024; **5**, 10. https://doi.org/10.1051/vcm/2024012.