

Received date: Jan 22, 2019

Accepted date: Jan 26, 2019

Published date: Jan 28, 2019

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Circulating Tumor Cells: One Step Ahead of Precision Medicine

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Commons CC-BY 4.0**Editorial**

1869 was the year in which Thomas Ashworth identified cells similar to cancer cells in peripheral blood [1]. Since that first observation, the medicine has made steps forward in the last years. Tumor derived cells found in the circulatory or lymphatic system are called circulating tumor cells (CTCs). It is believed that CTCs are disseminated by primary tumors to initiate metastatic growth at distant organ sites [2]. CTCs are therefore considered important indicators of metastatic disease and prognostic biomarkers [3-5]. Together with cell-free nucleic acids and exosomes found in peripheral blood and other body fluids, they fall within the liquid biopsy, a simple, non-invasive and low-cost diagnostic systems that are able to drive medical decisions and implement precision medicine [6].

CTCs are extremely rare in peripheral blood [7]. They do not have well defined morphological aspects [7]. Moreover, they can cluster together or with leukocytes, platelets, endothelial cells or fibroblasts, having thus survival advantage and protection from the immune system and oxidative stress [8-10].

The Cell Search system is the only technique approved by the US Food and Drug Administration for the detection and enumeration of CTCs in metastatic breast, colorectal, and prostate cancers in the clinical setting [11-14]. This method exploits the over expression of the epithelial cell adhesion molecule (EpCAM) present only in epithelial cancer types [7]. However, in this way CTCs originating from mesenchymal tumors or CTCs are undergoing epithelial-mesenchymal transition (EMT), the process that sustains both CTC migration and extravasation towards secondary sites, escape [15]. Therefore, other techniques for exactly detecting CTCs are necessary. At present, several systems based on CTCs properties are available to detect and isolate them from leukocytes [16]. Thanks to large size (up to 20-30 μm), mechanical plasticity, and dielectric mobility properties compared with blood cells [17-20], CTCs can be isolated through membrane filtration, density gradient stratification, dielectric mobility, photoacoustic and microfluidic separation [21-23]. However, these techniques have a low specificity [24]. Other methods exploit a specific protein expression such as cytometric high-throughput imaging, immunomagnetic separation [25] and negative leukocyte depletion [26]. Here too, there are several restrictions: there are no specific antibodies to use. EPCAM, regarded as a biomarker reflecting a risk factor for tumor recurrence [12], cytokeratins (CK8, CK18, CK19) [27] and specific tumor markers [28-30] are also useful for detection and isolation. On the other hand, EPCAM is usually lost during EMT; moreover, CTCs may acquire a stem cell-like phenotype by expressing markers such as CD44, CD133, and aldehyde dehydrogenase, and both proliferative and self-renewal properties favouring metastatization in secondary tissues [31-32].

Now it is clear that for each patient CTCs are characterized by high heterogeneity [33]. Both primary tumors and metastases evolve over time in response to selective pressure of immune system and therapies [33]. This affects CTCs purification and analysis. For this reason, it is necessary to combine differential methods to isolate functionally heterogeneous CTCs.

Methods based on CTCs protein secretion, on migratory properties cultivating them in synthetic substrates, or CTC-derived organoids are emerging [25-34] in order to let CTCs in routine clinical practice. Of course in these models is not considered the contribution of the microenvironment, such as immune system and vascularization.

In a growing number of tumors, the absolute number of CTCs in a 7.5 ml blood sample is significantly associated with prognosis, giving to CTCs a prognostic value [35]. They can also be relevant both for primary diagnosis, for diversify malignant from benign lesions, for patients' therapy response and not only these [35]. Thanks to the ability to analyse their genomic and proteomic profiles, CTCs can provide information on the presence of molecular potential targets for pharmacological actions. Scientists could have information about DNA mutations, epigenetic changes and mRNA expression driving the development of patient-specific treatments [36].

Conclusion

Although methods for enrichment and isolation of viable CTCs have to be improved, characterization of such cells could help in targeting metastatic progression, micrometastasis, and disease relapse answering several important clinical questions.

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