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Editorial Open Access

Circulating Tumor Cells as Potential Biomarkers: Current Trends and Future Perspectives

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Editorial

Metastasis among the cancer patients results in poor prognosis and reduces overall survival drastically. Biomarkers of cancer are present in various body fluids and tissues which may be detected easily. Discovery of these biomarkers has led to tremendous improvement in diagnosis and clinical outcome of cancer patients. Circulating tumor cells (CTCs) are one such bio fluid based markers which have been extensively studied in current times as diagnostic, predictive and prognostic markers.

Tumor cells divide and proliferate rapidly at the primary site. Some cells may get dislodged from the margins of the tumor, invade the blood vessels in the vicinity, travel through the blood stream, extravasate into a new target tissue and re-establish themselves in the new environment resulting in metastasis. They may also return to the site of primary tumor causing recurrence or relapse locally [1]. These cells in the blood stream are called as Circulating tumor cells [2].

Thomas Ashworth, a pathologist from Australia was the first to hypothesize that some cancer cells are prerequisite for metastasis in 19th century [3]. It was Isaiah Fidler in 2003 who coined the term CTCs. It is still unclear whether these cells are responsible for metastasis [4].

There may be 5 to 50 CTCs per tea spoon of blood [5]. CTCs can be easily detected in the blood of patients with advanced disease. However, their detection in early stages of cancer is challenging and is still being explored [2].

They may be loose or may cluster with other blood cells forming microclusters [1,2]. They are larger than leukocytes and may get trapped in smaller capillaries. Only CTCs which are small and highly plastic may be found in circulation [6]. In addition, different types of solid tumors may have different patterns of metastasis. Thus the site of sample collection may be critical [4].

Researchers believe that these cells harbor genetic information of the parent tumor cells which helps in diagnosis. CTC detection can be used as an adjuvant for TNM staging and biopsy. Biopsy and histopathologic examination involves a more invasive procedure than collection of blood sample [2].

The detection of circulating tumor cells in patients itself means that the prognosis is poor or it may suggest metastasis or recurrence, thus helps in predicting the prognosis as predictive markers [2]. In addition, determination of the number of CTCs before and after cancer therapy might help in monitoring the progress during the course of treatment as pharmacodynamics markers [2]. Changes in CTCs number during therapy may predict survival outcome thus highlighting the possible role of CTCs as surrogate end-point markers. Patients with CTCs ≥ 5 per 7.5 ml of blood are considered to show lack of response to treatment while those with <5 CTC have been considered to show remission [7]. However, the question whether CTC numbers correspond or correlate with gold standards such as radiological imaging outcomes is still under research. In addition, targeting these cells might prevent the future development of metastasis. Thus they can also be potential drug targets [8].

Isolation and characterization of CTCs has gained a lot of attention in the present time. Various isolation and detection methods based on physical and biological properties have been developed to identify CTCs. CTCs are mostly found in the white blood cell fraction after centrifugation of blood sample. Since they are larger than leukocytes, size filtration methods can be used to isolate them [9,10]. Antibody based isolation techniques with magnetic fields have also been developed which are targeted against the epithelial cell surface markers such as epithelial cell-adhesion molecule (EpiCAM). Laser scanning cytometry after staining with anti EpiCAM and anti CD45 fluorescent antibodies is also used [11]. Cell search system is one such method using immune-magnetic bead based separation which provides robust, reproducible CTC counts [12].

More sensitive techniques to detect the nucleic acids on CTCs have been developed such as reverse time polymerase chain reaction (RT-PCR) [13]. Cytomorphic assay such as fluorescent in situ hybridization (FISH) or DNA/RNA extraction have emerged successful in recognizing CTCs [2]. CTC-chip based on microfluidics and immune-magnetic cell capture is a very promising diagnostic tool [14].

CTC research in cancers like breast cancer [15]. lung cancer, colorectal cancers [12] has provided some information into the process involved. Some studies have found that the genetic expression and phenotype of these cells may differ from the parent cells which may be challenging for diagnosis [16,17]. Not all but only a unique sub population of CTCs were found to exhibit lethal metastatic potential, also called as 'decathlon champions' [18]. Some authors believe that (EMT) Epithelial mesenchymal transition is essential for metastasis [19-21]. Cancer stem cells are a subpopulation of tumor cells which have characteristics such as tumor initiating property, self-renewal capability, high proliferative potential, high motility, increased invasiveness, resistance to apoptosis and hence difficult to target and eradicate [20,21]. Currently detection of CTCs is mainly

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based on epithelial markers only. Including both epithelial as well as mesenchymal markers for detection has been suggested for the same reason [19].

However, there are certain limitations doubting their importance as biomarkers [1,4]. Hurdles include filtration of large CTCs and micro clusters in smaller capillaries, cloaking of CTCs by platelets or coagulation factors, heterogeneity of CTCs due to EMT or possible stemness, and the of benign circulating epithelial cells which may cause hindrance. Various technical errors as in standardization of isolation and detection techniques, time of blood collection during course of treatment namely baseline and follow-up, time and site of collection of blood sample, discarding first few drops of blood collected to avoid contamination from skin cells, sample handling, transport and storage, type of antigen selected, optimizing antibodies, use of appropriate positive and negative controls also need careful monitoring [9]. In addition, rate at which the tumor cells enter the blood vessel, and may influence their detection. Their detection in in early stages of cancer is also questionable.

Though their role is vastly studied in breast and lung cancer, role of CTC in other types of cancer such as head and neck cancer, melanoma, pancreatic cancer, biliary cancer and so on is yet to be elucidated. Further research in isolation and characterization of CTCs may provide more information to prove their role as biomarkers as well as novel therapeutic targets.

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