

Circulating Tumor Cells – Cutting Edge Research?

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“Circulating Tumor Cells (CTCs)”, shed into the bloodstream from primary and metastatic tumors are regarded as the liquid biopsy of cancer is an enthusiastic field of research which attracted half-a-thousand publications in the recent two decades. CTCs were first reported in the blood of a dead cancer patient in 1869 [1]. The CTCs research can be categorized into three major aspects: 1) Clinically focused on the applications of CTCs as biomarkers for cancer diagnosis, progression, prognosis and therapeutics; 2) Molecular characterization of CTCs to determine their clinical relevance and functional activities in tumor microenvironments; and 3) Technological investment in detection and isolation of rare CTCs from peripheral blood specimens and even in vivo tracking of CTCs.

The current chemistry of CTC analysis is, as applied by the only FDA-cleared CellSearch[®] system and other platforms, mainly relied on differentiating live epithelial cells from peripheral CD45+ leukocytes, by using epithelial makers, such as EpCAM, CK 8, 18 and 19 in addition to viability DAPI marker [2]. Based on this principle, high CTC numbers have been correlated with increased metastasis and decreased time to relapse, which supporting the predictive values on cancer progression, prognosis and survival in several cancers [3]. A meta-analysis of 49 eligible studies enrolling 6,825 breast cancer patients indicated CTC a stable prognostic biomarker at both early- and metastatic stages [4]. Such encouraging reports have directed many investigators into the search of various strategies in CTC enrichment to achieve the limit of detection at one CTC per million cells level. According to Hong and Zu [5], from the year 2004 to 2012, at least 14 microdevice platforms have been developed following the CellSearch[®], and they have competed with each other for the clinical sensitivity, specificity, viability, recovery and purity. Some investigators even intended to develop a single platform that is able to detect all cancers [6]. However, the approach of using epithelial markers may cause false positives such as wrong identification of benign circulating epithelial cells, otherwise more importantly omitting the biological features of CTCs such as heterogeneity, subpopulational stemness, partial epithelial-mesenchymal transition, and seeding potential [7]. Alix-Panabieres and Pantel [2] has emphasized the important interplays between Epithelial-Mesenchymal Transition (EMT) and Mesenchymal-Epithelial Transition (MET) in cancer disease, which may influence the moiety of molecular expression in relation to dedifferentiation property and cell plasticity. Have the CTC research gone too fast? What are the real challenges? Several important hurdles about CTCs remain unsolved. One is the biophysical factors such as trapping at the capillary pores that leads to only a minute amount and/or plastic CTCs to be present in the circulation [7]. This at least partially explains why application varies due to the tumor origin, for example CTCs can be detected in early-staged breast tumors but cannot in colorectal tumors. In patients with colorectal cancer, the CTCs recovery was shown to be more efficient in mesenteric blood than peripheral blood, suggesting that CTCs as biomarkers may require more invasive ways rather than the minimally invasive venipuncture depending on the tumor site [8]. In order to further break through the CTC enrichment and its detection, researchers may have to go a bit back to the basic science, i.e. the characterization of the real CTCs rather than the “circulating epithelial cells”. This would require the help of cutting-edge technology for viable CTC isolation that allow the culture and analysis of primary cancer cells [9]. Last but not the least, an in vivo enrichment in the

arm vein of patients has been described and shown to enrich 10 times the sensitivity for CTC detection [10]. This has primed the idea of real-time in vivo tracking of CTCs by imaging techniques and also possibly therapeutic targets, in near future, especially when the specific fingerprints of CTCs are decoded.

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