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Mini Review

Current Clinical Applications and Challenges of Circulating Tumor Cells

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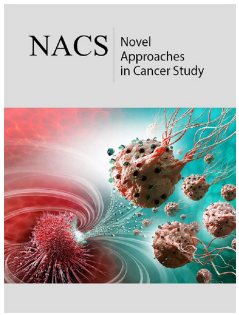

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Abstract

Analysis of circulating tumor cells (CTC) has received enormous attentions for its potential to obtain diverse information of tumors dynamically. Nowadays fast-developing detection technologies facilitate its biological research of tumor dissemination and clinical implications. This review is going to discuss clinical applications of CTC including prognosis and prediction of metastatic progression, surveillance of therapeutic response and identification of therapeutic targets and resistance mechanisms and to further introduce present detection technologies of CTC.

Keywords: Liquid biopsy; Circulating tumor cells; CTC

Abbreviations: CTC: Circulating Tumor Cell; CRPC: Castration-Resistant Prostate Cancer; NSCLC: Non-Small Cell Lung Cancer; CI: Confidence Interval; CDX: CTC-Derived eXplant

Introduction

Currently, circulating tumor cell (CTC), a crucial intermediate of metastasis from primary tumor to distant organ sites [1], has arisen enormous attention for its obvious diagnostic, prognostic and predictive potential for personalized medicine. Through dissemination of tumor cells to distant organ sites in bloodstream, it has been demonstrated that CTC can gain key characteristics required for metastasis such as recruitment of immune cells, inflammatory chemokines and cytokines, while still facing significant barriers including physical stress, oxidative stress and anoikis, resulting in its short half-life [2]. It is noted that not only CTC numbers can be quantified, but also changes in DNA, RNA, and protein levels describe multiple heterogeneities compared with nonmalignant cells. And present studies have proposed that both single CTC and CTC clusters contribute to metastasis and CTC clusters with epithelial and mesenchymal phenotypes may be more metastatic than single cells [3].

We are going to further discuss the clinical applications and detection technologies concerning CTC which attracts tremendous interests in the medical frontier from three aspects including prognosis and prediction of metastatic relapse and mortality, surveillance of therapeutic response and identification of therapeutic targets and resistance mechanisms.

Clinical Applications of CTC

In this review, we collected published original research articles (impact factor, IF>10) in Pubmed in the recent three years and classified researches in each application subset (Figure 1) [2,4-57]. In consistent with its metastatic characteristics, we found that CTC might be more applicable in prognosis and surveillance of metastatic cancer rather than early cancer screening.

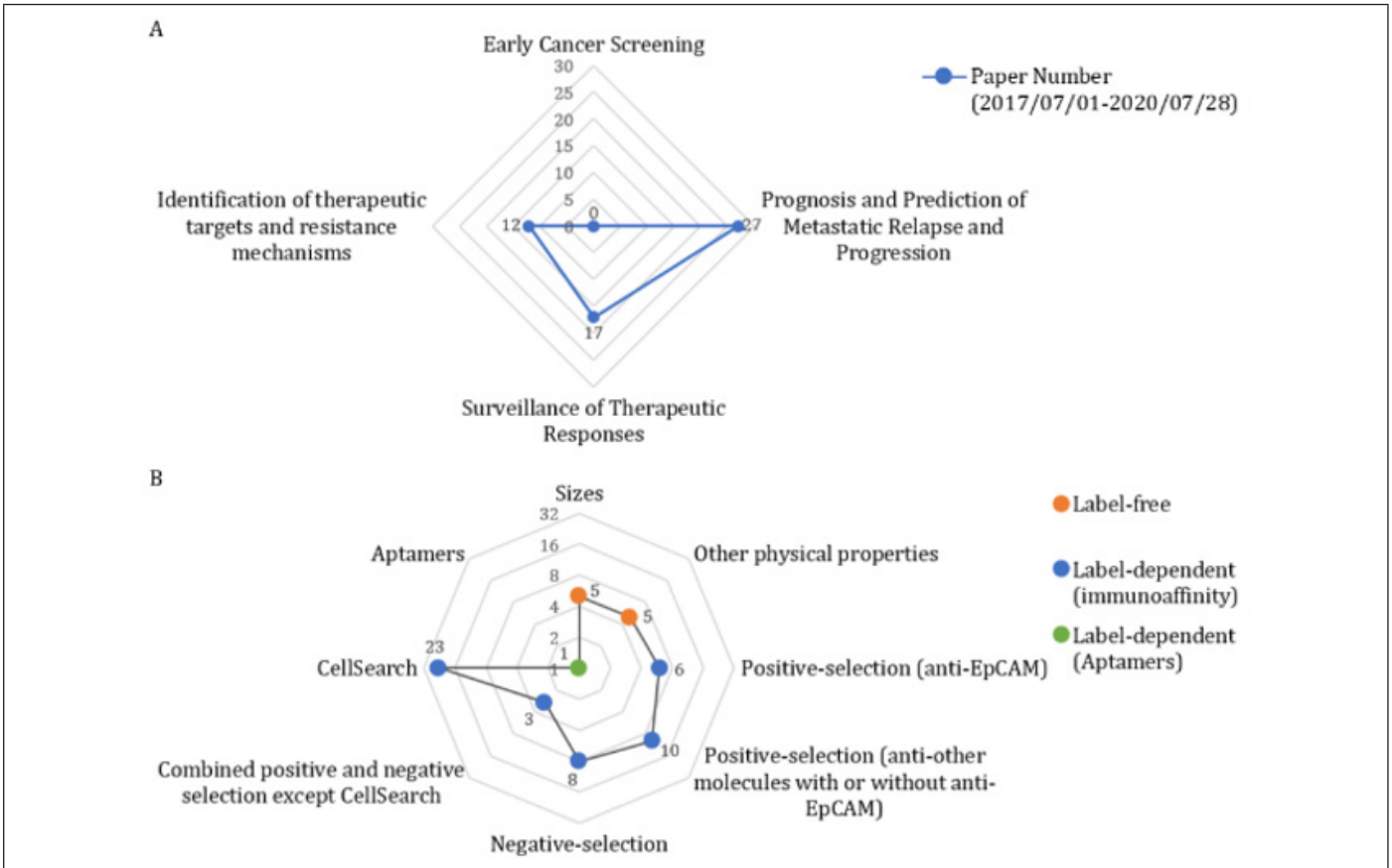

Figure 1: CTC-related publications counting via PubMed in the recent there years (IF>10).

A. Comparison of published paper amount on early cancer screening (0), prognosis and prediction of metastatic progression(27) [4,32-57], surveillance of therapeutic responses(17) [15-31], and identification of therapeutic targets and resistance mechanisms(12) [2, 4-14], respectively.

B. Comparison of published paper amount on different CTC-enrichment methodologies: size(5)[2,4,13,42,48], other physical properties(5)[10, 36, 64-66], positive selection(anti-EpCAM, 6)[19,22,34,43, 50,55], positive selection(anti-other molecules with or without anti-EpCAM, 10)[7,19,24,28,45,46,69,72], negative selection(8) [6,8,10,20,23,29,41,65], combined positive and negative selection expect CellSearh(3)[12,21,67], CellSearch(23) [5,9,11,15,17,25 27,32,35,37,38,44,47,49,51-54,56,77,78], and aptamers(1) [68].

Prognosis and prediction of metastatic relapses and progression

There are a number of studies presenting the compelling correlation between CTC and prognosis in patients with various tumor types, especially for assessment of survival in clinical trials. Netterberg's team demonstrated that CTC counts could be useful for early predicting Overall Survival in patients with metastatic colorectal cancer [58]. Also in non-small cell lung cancer (NSCLC), one recent study said higher pretreatment CTC and persistence of CTC posttreatment were significantly associated with elevated risk of recurrence outside the targeted treatment site in patients with early-stage NSCLC treated with stereotactic body radiotherapy [39], while another retrospective assessment showed that cerebrospinal fluid CTC was correlated with risk of death (Hazard Ratio: 3.39, 95% confidence interval(CI): 1.01–11.37; P=0.048) in patients with leptomeningeal metastases from NSCLC [55], while . Not only CTC quantification are associated with prognosis, but also the compounds in CTC can be prognostic biomarkers. It was reported that out of 47 patients with aggressive variant prostate cancer from whom 257 individual CTC were sequenced (1-22 CTC/patient), twenty (42.6%) had concurrent 2+ tumor suppressor genes losses in at least one CTC in association with poor survival and increased genomic instability, inferred by high large-scale transitions scores [14].

Surveillance of therapeutic responses

At present, a large number of researches stated that CTC counts, and its molecular analysis could predict and monitor drug responses in metastatic cancer [4,27,29]. For example, in castration-resistant prostate cancer (CRPC), CTC increases were associated with worse prognosis, suggesting alternative therapies after three cycles of chemotherapy [59], and another Phase III clinical trial reported CTC number could serve as a response measure of Prolonged Survival for metastatic CRPC [16].

Identification of therapeutic targets and resistance mechanisms

In the past few years, characterizing of rare, heterogeneous CTC greatly provides thorough insight into metastasis and helps

develop novel targeted therapies particularly by high throughput sequencing. Franses and their colleagues identified stemness gene LIN28B expression in CTC is prognostic for pancreatic ductal adenocarcinoma by RNA-seq and investigated LIN28B molecular mechanism on metastasis [60]. Recently, single cell sequencing enables to monitor mutation status for therapeutic resistance [4] and identify DNA methylation remodeling from CTC cluster to single CTC which was proved to enhance metastasis [61]. According to these excellent findings, molecular characterization of CTC provides a unique opportunity to determinate drivers of dissemination and guide prospective treatments targeting the "seeds" of metastasis. In addition, CTC-derived eXplant (CDX) and a CDX-derived cell line established by CTC are promising tools for exploring new strategies on metastasis or drug-resistance [61,62].

Detection Technologies of CTC

In practice, both single CTC and CTC clusters are extremely rare in blood, detection technology which directly determines its abundance and purity is the most challenging part for thorough biological studies and clinical applications as well of CTC. In order to increase the concentration of CTC by several log units, a great many enrichment methods have developed rapidly which can be divided into two main groups: label-free methods based on invasive capacity or physical properties such as size, deformity and density, or label-dependent ones including positive or negative selection depending on the immunoaffinity [63]. Particularly, CellSearch approved by FDA have been widely applied in dozens of clinical trials (Figure 1) [2,4,6-8,10,12,13,19-24,28,29,34,36,41-43,45,46,48,50,55,64-72]. Nowadays, current strategies are prone to develop devices combining antibody cocktails with advanced techniques like immunomagnetic beads, nanoparticles or microfluidics to isolate and identify CTC for higher specificity and sensitivity [3,73,74].

Discussion and Outlook

CTC displaying similar molecular properties of primary tumor tissues and additional metastatic-associated changes can reveal the biology of the tumor dissemination that has not been clearly elucidated yet and guide the diagnosis, prognosis, monitoring and treatment of metastatic diseases. Due to its noninvasive and repeatable features, it has been validated as diagnostic and prognostic surrogates of tissue sampling and predictive indicators of recurrence and resistance for efficient therapeutic interventions [4,75]. Cancer screening at an asymptomatic stage always starts with determining the regulation in retrospective case-control trails and then setting cohort trails containing large populations requires long follow-up time to validate it. Practically, only few studies evaluated CTC as a biomarker for early cancer detection because it takes time for tumor cells to progress from primary site into blood and CTC might be zero or extremely low at an early stage. However, one group reported that CTC allowed early diagnosis of lung cancer in patients with chronic obstructive pulmonary disease [75], and another preliminary study has estimated that their CTC detection method based on RNA signature could enable a noninvasive early diagnosis of hepatocellular carcinoma in populations where viral hepatitis and cirrhosis are prevalent [76]. Though focusing on a population with high risk of developing cancer could speed up the long validation process, these studies need large further cohort to provide more evidences.

The biggest obstacle of CTC is its detection technologies. Basically, the heterogeneity in phenotypes and genotypes has made it challenging to directly capture CTC and raised the question whether the panel that we use to identify CTC is sensitive and specific enough for a certain tumor type. Label-free and aptamers-dependent methods are novel isolations means that can overcome this shortage to some extent, but the potential applications of some highly sensitive detection methods need clinical trials with larger population to validate. More importantly, it is essential to evaluate and establish criteria for the clinical utility of CTC to assure its efficacy [77,78].

In spite of these challenges, these exciting findings on CTC highlight its crucial role during metastatic process as well as its significant application value of predicting prognosis or drug-responses and developing novel therapeutic strategies. We believe that CTC with these outstanding advantages promise to have a bright future.

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Conflicts of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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