



Primary and Secondary Circulating Prostate Cells: Theoretical Considerations and Clinical Utility

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Short Communication

Although circulating tumor cells were first reported in 1869; [1] it has not been until the last few decades that technological advances have permitted an improved detection and isolation of these rare cells from the blood.

Early in prostate cancer, there is at least one sub-population of cells that disseminate firstly to the neurovascular structures and then into the circulation [2]. These have been defined as primary circulating prostate cells (CPCs) that are those detected before initial therapy. These primary CPCs enter the circulation in two forms; a) passively as a result of vessel leakage caused by the growing tumor and these cells do not require specific phenotypic characteristics [3] or b) actively whereby the CPCs are capable of detaching from the surrounding cells, survive in this free state, migrate to the blood vessels, cross the endothelial barrier and enter the circulation [4]. Thus primary CPCs consist of a heterogeneous population ranging from metastatic initiating cells with specific cell properties to non-aggressive cells without any specific survival ability [4]. Active dissemination is a result of decreased expression of anchor proteins, such as E-cadherin, Beta-catenin and cytokeratins [5,6], increased expression of matrix metalloproteinases [7] and increased expression of mesenchymal markers such as N- or O-cadherin and vimentin, the epithelial-mesenchymal transition [8]. The specific phenotypic characteristics of the cancer cells will determine their ability to disseminate into the blood stream and may not reflect the general characteristics of the primary tumor.

In order to implant in distant sites the CPCs must survive the shear forces of the circulation and evade the immune system, with an estimated 0.01% of all circulating tumor cells survive to produce distant metastasis [9]. The phenotypic characteristics of primary CPCs also may play a role in whether tumor cells implant in distant tissues. Primary CPCs expressing the tumor suppression protein CD82 have been detected in blood but were associated with a significant decrease in bone marrow micro metastasis in comparison with CD82 negative primary CPCs [10].

Once implanted these cells must evade the immune system and interactions with tissue stromal cells. CPCs home into the hematopoietic stem cell niche in the bone marrow, this microenvironment consists of many different cell types where they are protected against therapeutic intervention [11]. Here cells undergo the mesenchymal-epithelial transition [12], the reversal of the previous process. Stromal-tumor cell interactions may change the phenotypic expression of the tumor cells; MMP-2 expression has been shown to decrease in bone marrow micro metastasis [13]. Once implanted in the bone marrow niche there is a variable period of dormancy, however, with time prostate cancer cells may switch to a proliferative phenotype [14], resulting in metastasis formation and dissemination of secondary CPCs.

CPC detection

There are a vast number of techniques that have been developed for the detection of circulating tumor cells, which has hindered the comparison of different studies and the consensus of defining these cells. Each method has differing advantages and disadvantages and has been extensively reviewed [15,16].

Clinical Utility

Primary CPCs: if as predicted, these cells disseminate early in the development of cancer but not all these cells will survive, implant and produce metastasis then their detection could be useful in the early detection of prostate cancer but not as a prognostic factor. There is limited evidence in the scientific literature, and differing detection methods have produced very different detection rates. The detection method will define what is being detected and this has to be put in the clinical context of what is known about prostate cancer.

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Received Date: 14 Sep 2017

Accepted Date: 13 Nov 2017

Published Date: 24 Nov 2017

Citation:

Murray NP. Primary and Secondary Circulating Prostate Cells: Theoretical Considerations and Clinical Utility. *Clin Oncol.* 2017; 2: 1372.

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Using the EpCAM based CellSearch® detection system there was no association between CPC detection and the clinical parameters in men with prostate cancer prior to surgery, nor between men with an increased serum PSA and diagnosed with prostate cancer or benign disease [17,18]. In men with localized prostate cancer only 20% were found to be positive using the Cell Search System® [19]. The Cell Search System® detects epithelial cells (EpCAM and cytokeratin positive cells) and does not distinguish between benign and malignant cells. Using this detection system circulating cells have been reported in benign conditions [20] and this may be one reason why the detection system failed to differentiate between men with prostate cancer and benign conditions. CPCs have been reported in men with benign disease, but unlike patients with prostate cancer these benign CPCs do not co-express P504S [21]. In this context using a telomerase and anti-Ber-4 CPCs were detected in 80% of men with localized cancer [22], while using a combination of anti-PSA and anti-P504S in over 1000 men undergoing prostate biopsy for suspicion of prostate cancer a sensitivity of 81%, specificity of 89% and a negative predictive value of 90% [23]. Thus the detection of primary CPCs could be useful in decreasing the number of unnecessary prostate biopsies, especially as in men with low grade small volume cancers primary CPCs are not detected [24].

However, as a prognostic biomarker the detection of primary CPCs has limited value; using the Cell Search system® only 11% of men with positive pre-surgery and there was no associated with treatment failure [25]. Nor was there improvement in incorporating the detection of primary CPCs with the CAPRA score to predict treatment outcomes [26], but men primary CPC negative had a better prognosis [27]. Those men who were positive for primary CPCs but became negative after radical prostatectomy had a better prognosis than those who remained CPC positive [28].

b) secondary CPCs are those detected after primary treatment and differing from primary CPCs have been reported to have prognostic significance independent of the method used to detect them. This holds for both non-metastatic and metastatic prostate cancer. The frequency of secondary CPC increases with disease progression [29], however with Cell Search® in high risk non-metastatic cancer few patients are deemed to be positive, even when using a 1 cell detected per sample cutoff value [30]. Using the Epispot® or CellCollector® systems one third of patients were found to be positive in high risk non-metastatic prostate cancer and were associated with pre-surgery PSA values and clinical tumor stage [31]. Secondary CPCs predict biochemical failure in men after radical prostatectomy and without evidence of disease; there is an association with the clinic-pathological findings and men positive had a shorter time to failure [32].

In metastatic prostate cancer, the presence of CPCs has been reported to be an independent prognostic factor, associated with worse survival, and as a marker of treatment response in men with hormone sensitive and castrate resistant prostate cancer [33-36]. More recently the phenotypic characteristics of secondary CPCs have been used to determine treatment; the expression of the androgen receptor variant Arv7 in CPCs has been associated with resistance to abiraterone and enzalutamide [37].

The future: the majority of early studies were focused on methodology of CPC detection and enumeration of CPCs. With improving technology, CPC recovery and characterization has become more accurate and cost-effective. It will be important to discover whether molecular profiling of CPCs may aid in the clinical

decision making process, offering utility in directing targeted therapy in high risk patients, while not over treating those patients with very low risk of therapy failure.

In summary: primary and secondary CPCs have different clinical utility, primary CPCs being associated with the detection of cancer but not as a prognostic factor, while secondary CPCs are associated with prognosis and may have utility in guiding therapy options.

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