Early during the formation and growth of a primary tumor (e.g., breast, colon, or prostate cancer), cells are shed into the blood vessels. These circulating tumor cells (CTC) can be detected via different technologies based on their physical and biologic properties. Detection and molecular characterization of these CTCs are among the most active areas of translational cancer research, with more than 400 clinical studies including CTCs as a new biomarker and considering such blood analyses as a real-time liquid biopsy. Aims of research on CTCs include (i) estimation of the risk for metastatic relapse or metastatic progression (prognostic information), (ii) stratification and real-time monitoring of therapies (predictive information), (iii) identification of therapeutic targets and resistance mechanisms, and (iv) understanding metastatic progression in patients with cancer (1, 2). The clinical relevance of CTCs in prostate cancer has been recently reviewed (3). In general, several studies have indicated that CTC counts predict the prognosis of patients with metastatic prostate cancer, whereas the relevance in patients at earlier stages remains to be determined. However, CTCs are not part of the routine clinical management yet. Recently, Danila and colleagues (4) have outlined necessary steps to qualify specific CTC tests for medical decision making in clinical practice or drug development. The detection of CTCs in the peripheral blood of patients with cancer holds great promise, and many exciting technologies have been developed over the past years (1, 2). However, detecting CTCs remains technically challenging. CTCs occur at very low concentrations of one tumor cell in the background of millions of normal hematopoietic cells. Their identification and characterization require extremely sensitive and specific analytical methods, which are usually a combination of enrichment and detection procedures. CTC enrichment includes a large panel of technologies based on the different properties of CTCs, including physical properties (size, density, electric charges, and deformability) and biologic properties (surface protein expression and viability; refs. 1, 2). After enrichment, the CTC fraction usually still contains a substantial number of leukocytes, and CTCs therefore need to be identified by a well-defined method that can distinguish tumor cells from normal blood cells at the single cell level: mRNA- or protein-based strategies. At present, CTC detection is focused on the development of microfluidic devices called CTC-chips, which can handle very small blood volumes. The first CTC-chip consisted of an array of anti-EpCAM antibody–coated microposts (5) and has been further developed into a herringbone (HB) structure. In this issue of Cancer Discovery, Miyamoto and colleagues (6) have used this 106CTC-chip to analyze CTCs in patients with advanced prostate cancer. In metastatic prostate cancer, androgen deprivation therapy (ADT) is recommended as a first treatment, and secondary hormone therapies are used to suppress androgen receptor (AR) activation in patients with castration-resistant prostate cancer (CRPC). Using the 106CTC-chip to capture and detect CTCs, Miyamoto and colleagues (6) show that the activity of the AR pathway may be monitored through an immunocytochemical characterization of CTCs via a new established quantitative immunofluorescent assay based on the expression of the AR-regulated genes encoding prostate-specific antigen (PSA) and prostate-specific membrane antigen (PSMA). PSA and PSMA are upregulated following AR activation and AR suppression, respectively. Moreover, they define 3 different CTC patterns: “AR-off” for PSA+/PSMA−, “AR-mixed” for PSA+/PSMA+, and “AR-on” for PSA−/PSMA+. Miyamoto and colleagues have studied the clinical relevance of this AR characterization in CTCs in 2 patient cohorts: (i) patients with untreated metastatic prostate cancer and (ii) patients with CRPC. Indeed, the initiation of ADT in
The Potential of Circulating Tumor Cells as a Liquid Biopsy to Guide Therapy in Prostate Cancer

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