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Commentary

Arterial or Venous: Where Are the Circulating Tumor Cells?

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The study of circulating tumor cells (CTCs) has been largely confounded by the low number of these cells in the blood stream amid billions of other cells. To overcome this challenge numerous methodologies for CTC isolation have been described. Photoacoustic flow cytometry (Nedosekin et al., 2013), dielectrophoresis array (Maltoni et al., 2015) and microfluidics (Warkiani et al., 2015) are among the most sophisticated of these methodologies. However, methods based on immunecapture and immunestaining are still the more frequently utilized, with CellSearch® remaining the most commonly used method to date and the only US FDA approved (Alix-Panabieres and Pantel, 2014).

Irrespective of the method of isolation and detection used most studies fail to detect CTCs in the numerous cases. This is particularly unexpected in studies of cases with metastatic disease, in which patients with substantial tumor burden have been found with undetectable CTC levels.

The lack of detection of CTCs is usually attributed to limitations on the methodologies utilized such as the conditions of collection and treatment of the samples, the cell size, clustering of CTCs and the high phenotypic plasticity of cancer cells. One common concern is the lack of epithelial markers in disseminating carcinoma cells that experienced epithelial-to-mesenchymal transition (Rao et al., 2005). Moreover, the low number of CTCs usually detected, 1–10 cells in 7.5 ml of blood, is susceptible to stochastic distribution in the sampled blood.

The study by Terai and colleagues published in *EBioMedicine* provides an alternative explanation to this lack of CTCs (Terai et al., 2015). The authors compared the number of CTCs in arterial and venous blood samples from patients with metastatic uveal melanoma. CTCs were detected in all patients when arterial blood was analyzed and the number of CTCs ranged from 1 to 168 cells in 7.5 ml of blood, with 35% of cases presenting more than 10 CTCs. In contrast only 53% of cases were found positive for CTCs when venous blood with interrogated and CTC counts ranged from 1 to 8 cells. These findings are supported by previous observations that more CTCs were detected in right atrial blood than in peripheral venous blood in patients with hepatocellular carcinoma (Fang et al., 2014). Similarly, CTCs were found at higher number localized to the hepatic portosystemic macrocirculation than in peripheral blood (Jiao et al., 2009).

These results suggest that venous blood might not be the ideal source of CTCs. Venous blood not only has been filtered through the lung, but also has been carried through the arteries into the tissue capillary bed before being sampled. It is likely that circulation through the capillary network significantly affect the CTCs. First, it is commonly acknowledged that CTCs are larger than most blood cells, less deformable and frequently travel in clusters (Aceto et al., 2014). However these cells must transverse through narrow capillaries to reach venous circulation. For normal blood cells the shear stress is five times higher in arterioles and capillaries than in major arteries or veins (Papaioannou and Stefanadis, 2005), and possible many folds more for CTCs. All of these pose significant trauma in these cells and are likely to result on activation of the stress response and phenotypic changes. Second, the most "dangerous" CTCs are those pre-programmed for migration and invasion, the capillary beds provide the right environment for tissue penetration, even when this process does not result in the seeding of micrometastases. The latter would also result on substantial loss of functionally significant CTCs. Third, the low oxygen tension and nutrient depravation in venous blood could affect CTCs, from compromising cell viability to changing their phenotype. While the consequences of these phenotypic changes are unclear, they could potentially affect the capacity of many of the current methodologies to detect these cells. Future studies owe to explore whether there are phenotypic differences between CTCs isolated from venous and arterial blood.

Despite the mounting evidence supporting the use of arterial blood, it is unlikely that this will be widely applied in clinical settings. Arterial blood sample collection is usually more painful than regular venipuncture. Patients may experience moderate discomfort and longer compression is required to prevent bleeding from the site. Although arterial blood is routinely collected for determining arterial blood gases and pH, it is a more dangerous procedure requiring in depth training beyond the routine phlebotomist skills. Moreover, in studies requiring sequential sampling, such as those for monitoring therapy response, patient retention might be compromised if arterial blood collection is implemented.

Nevertheless, the findings by Terai and colleagues that arterial blood is a better source of CTCs than venous blood need to be considered when

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planning projects involving CTCs. In particular, this will be important in studies involving single cell analysis for genetic or phenotypic profiling, where a reasonable number of CTCs per case need to be analyzed to provide relevant clinical information.

Disclosure

The author declares no conflicts of interest.

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