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Mini Review

The Acoustic Technology for Ctcs Isolation in Blood: Low-Cost Devices

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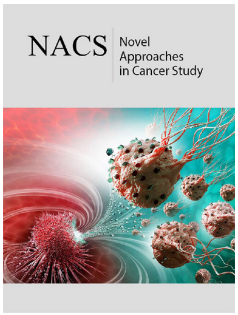

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Abstract

Blood samples can be used as a liquid biopsy in cancer diagnosis and chemotherapy monitoring. This label-free method offers benefits over traditional tissue invasive biopsy. It is possible to separate rare cells from blood samples by Ultrasounds on the basis of their physical properties in a biocompatible manner. A successful separation of cultured cancer cells from WBCs with acoustic-based methods is being demonstrated during the last years through different technological approaches. The concept of plate acoustic waves (PAW) applied to acoustophoresis was recently introduced to perform acoustic flow-through separation of rare cells in blood samples. It lies in the geometrical chip design, different to other micro separators (BAW and SAW). This new strategy allows soft materials of extremely reduced volume and low-cost fabrication and opens a door to printing manufacturing processes.

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The use of blood samples as liquid biopsy for cancer diagnosis offers benefits over traditional tissue biopsy. Tumor cells are shed from primary distant sites in the bloodstream to circulate, becoming biomarkers of interest for cancer prognostics, monitoring treatment response in personalized medicine and contain information about possible specific mutations of a tumor Thus, isolation of viable circulating tumor cells (CTCs) is essential for liquid biopsy, which has shown to be an efficient alternative to tissue biopsy [1]. Chemotherapy and other therapy treatments, as well as mechanisms of treatment resistance can be monitored through the analysis of CTCs. However, isolation of CTCs from blood is nontrivial due to their extreme rarity in comparison to the blood cells [2].

Several attempts have been developed during the last decade to address it. Numerous microfluidic platforms are being developed during the last decade for isolating and capturing CTCs However, new devices for high-throughput CTC detection and isolation is still demanded. These systems must meet five goals to isolate viable CTC of a high-purity for clinical applications: the highest efficiency, purity, sensitivity, cell viability and throughput-speed. In addition, new low-cost approaches are required for translational clinic applications of diagnostic and monitoring. High purity is in strong demand for CTC enumeration, molecular characterization, and functional assays with less background intervention from WBCs.

Microfluidic devices provide numerous advantages over conventional methods associated to a reduction of the device size and simplification of protocols commonly used to perform cell sorting. These systems can be roughly classified into two groups, one of them comprises affinity-based methods that use surface markers, such as EpCAM, to distinguish CTCs from their surrounding blood cells. Studies performed on cells forming a tumor have demonstrated that epithelial tumor cells exhibit epithelial properties and express on their surface molecules of epithelial origin [3,4]. While these methods show very good specificity, they are hindered from false-negatives due to downregulation of the expression of surface markers on some CTCs which are undergoing epithelial–mesenchymal-transition (EMT) [3].

Many other strategies for detecting CTC in peripheral blood use differential physical cell properties in order to distinguish CTC from blood cells, including the cell size (epithelial cells) [4] their shape, deformability and/or density differences of CTCs and white blood cells (WBCs) and electrophoresis platforms [5]. These size-based are label-free methods, which

include hydrodynamic and cross-flow filtration [6,7] using spiral channelization [8-13] channels that incorporate contraction/ expansion reservoirs for pinch alignment of the cells, micropillars [14-16], micro-scale vortices [17,18], serpentine microfluidic channels [19,20] or membrane microfilters [21] with pore diameters chosen to have the dimension between the diameters of cancer cells and blood cells. Some of them base their work on a deterministic lateral displacement (DLD) [22,23]. inertial focusing systems [24-26] or micro post trapping [27].

The acoustic sorting method offers a means to separate cells on the basis of their physical properties in a label-free, contactless, and biocompatible manner. A successful separation of cultured cancer cells from WBCs with acoustic-based methods was recently demonstrated in some microfluidic platforms using Bulk acoustic waves (BAW) and Surface acoustic waves (SAW) [28-30], applied either on cultured cancer cells or tumor cells in spiked blood samples respectively. These methods base their actuation on processes of differentiated cell enrichment induced by ultrasounds on flowing samples, involving mass transfer processes between parallel flows in some cases. The acoustic force is used to drive and collect target cells operating on size, density and compressibility of different cell populations. In a recent work we have successfully demonstrated the separation of CTCs from blood samples based on cell size [31] using Plate acoustic waves (PAW) of the thin structure of the chip. In our work, we reported a three-flow microfluidic (3FM) system established in a low-cost polymeric chip for the separation of CTCs with high purity based on the application of ultrasounds. The acoustic wave was strategically applied inside the channel along its central axis, where the TCs collected, leaving the blood cells circulating beside the channel walls to be separately extracted through different outlets. The microchannel takes advantage of a forced migration of cells [32] induced by the acoustic pressure gradient established. We evaluated the sensitivity and efficiency of CTC capture in a model system using blood samples from healthy donors spiked with tumor cell lines. 20 model system samples were tested for determining the recovery rate of the microdevice.

Conclusion

The acoustic technology for sorting purposes works at power intensities and frequencies similar to the ultrasonic imaging, with a little impact on the viability (high biocompatibility) [31,32] of the cells. It presents clinical advantages as does not require modification of the media, thus no labeling, maximizing the potential of CTCs to be maintained in their native states, cultured, and analyzed *in vitro* or *ex vivo*. This non-contact and label-free separation of tumor cells from blood enables their recovery regardless of their molecular profile. It offers the potential of early detection of cancer and micro-metastasis as well as noninvasive monitoring of the cancer patients undergoing treatment at a low-cost of fabrication, even allowing printing processing.

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