SURFACE ENHANCED RAMAN SPECTROSCOPY AND MICROFLUIDICS FOR RARE CANCER CELL IDENTIFICATION

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ABSTRACT

We have developed a combined microfluidics and Surface Enhanced Raman Spectroscopy (SERS) platform to identify individual mammalian cells on the fly. Cells, pre-labeled with SERS biotags, were injected in a flow-focusing microfluidic device and the Raman signature of each cell passing through the laser was acquired. We were able to identify the individual cells using a classic least squares fitting algorithm.

KEYWORDS: SERS, Microfluidics, Biotags, Circulating Tumor Cells

INTRODUCTION

Identifying and collecting rare malignant cells in bio-fluids has important diagnostic and prognostic implications [1]. It can be crucial to monitor the efficacy of drugs and treatments, as well as early identification of disease recurrence [2]. We previously reported a SERS platform to detect prostate cancer cells based on their overexpression of neuropilin-1 biomarker in which bright and spectrally rich SERS active biotags (SBTs), composed of a silver nanoparticle dimer core, were used to discriminate between healthy and cancerous cells [3]. The SERS signal originated for a cell is the superposition of many spectra from individual SBTs attached to the cell which act as barcodes easily distinguishable in the composite spectrum. The SERS intensities achieved are comparable to fluorescence [4]. We have also shown that with a similar SERS analytical approach we can detect and discriminate SBT-labeled polymer beads in microfluidic flow [5]. Here, we present our progress towards a powerful multiplexing platform that discriminates SBT-labeled object populations (beads or cells) that flow in a microfluidic disposable cartridge.

EXPERIMENTAL

The microfluidic device was designed based on Stiles et al. [6] such that the geometric design of side and middle channels determines the relative sheath and analyte mixture flow rates. The device was made of PDMS sandwiched between two microscope slides. Samples of either beads or cells, pre-labeled with SBTs, were injected in a microfluidic device and the SERS spectrum from each individual SBTs-tagged object flowing through the Raman laser was acquired. SBTs were synthesized according to previously published protocols [3,5]. Figure 1 shows a schematic of the experimental process.

A custom algorithm for spectra pre-processing and analysis was developed in-house using MATLAB. Classic least squares was performed to categorize the spectra. A model was generated based on reference
populations. Preprocessing including baseline subtraction and normalization was performed on all the spectra before analysis.

RESULTS AND DISCUSSION

Live cancer and normal cells were labeled with two sets of SBTs, one targeting the neuropilin-1 receptor of cancer cells, the other one being a positive control. The cells were injected into the microfluidic device and the spectra of individual cells was recorded as they flow in single file through the Raman laser. Figure 2 shows the results of the CLS analysis. The two populations can be clearly separated based on the NRP/PC, thus validating this approach to distinguish cell populations based on surface receptor overexpression.

Figure 3 shows the average SERS spectra for cancer and normal cells.

**Figure 2:** Box plots summarizing the statics for each cell population. Normal cells (blue dots) show much lower NRP/PC ratios thus making the detection of cancer cells (orange dots) tractable based on surface receptor overexpression.

**Figure 3:** Average spectrum of reference cancer and normal cells.
CONCLUSION

Here we present our progress toward a multiplexed SERS-based rare cell microfluidic cytometry platform. We showed that we are able to detect cancer and normal cells in flow, and to identify individual populations using CLS, by deconvoluting the Raman signatures of the SBTs.

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