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Research Article

Perpetual Enhancement of Circulating Tumor Cell Using Filtration Microfluidic Chip

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Abstract

Circulating Tumor Cells (CTCs) plays an important role in detection of cancer at early stage. CTCs indicate presence of tumor at primary stage or even in metastases. Separation of CTCs from blood is highly sensitive and difficult task as they are extremely rare (i.e., 1-5 CTCs per 10^9erythrocytes). There are some biochemical and physical methods to detect and separate CTCs from blood. To get pure and sensitive CTCs microfluidic lateral flow filtration (μ-LaFF) chip can be used. For separating CTCs gently lateral flow and vertical flow are combined in (μ-LaFF) chip. With the help of this method CTCs can be detected efficiently. And it becomes very easy to diagnose the cancer at early stage.

Keywords: *Circulating tumor cells(CTCs), Lateral flow filtration, Microfluidics*

1. Introduction

In blood tumor cells travel from primary tumor site to different parts and hence causes the spread of cancer. This travel is commonly known as Metastases. It can cause the death of patient. The detection of this Metastases is the most promising work because of their presence about one CTC per billion normal blood cells.

Some traditional ways to detect primary tumors are radiography (X-ray), magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound. Since these techniques are unable to give correct analytical data and are time consuming these are not acceptable. Hence currently affinity based technique is widely accepted. For this method anti-epithelial cell adhesion molecule (EpCAM) is used. It is induced in the microfluidic chip to capture the CTCs from blood. CTCs have to undergo Epithelial-mesenchymal transition in order to attack other metastases site, thus EpCAM level is regulated according this transition. There is slight possibility of regulating negative EpCAM. Hence it has some disadvantages also. Some label free techniques are useful because they only take tumor cells and does not effect on the red and white blood cells. They are impulsive. As it is filtered from red and white blood cells it should be designed carefully. To eliminate the losses from this a closed filtration system is adopted.
Here this paper presents microfluidic lateral flow filtration (μ-LaFF) chip to efficiently overcome spoiling of the tumor cells and blockage of the filter. As discussed earlier it separates CTCs gently by combining lateral flow and vertical flow. Lateral flow contributes to the movement of trapped cells from inlet to outlet. Whereas vertical flow applies pressing force on trapped cells. Hence this combination used to capture CTCs gently.

2. Materials and Methods

The μ-LaFF chip has a single inlet and a single outlet. The height of the channel in the chip is 40 μm. The filter gap varies from (8, 10, 12, 14 and 16 μ m) to obtain the flawless enrichment. There are around 1050 holes in the chip which ranges 25 to 100 μm and the distances vary from (100, 200 and 300 μ m) between each pair. This chip is manufactured by soft lithographic process.

This chip is coated with negative photoresist in Silicon wafer. And it has to undergo different processes such as soft baking, UV light exposure and post-exposure baking. After that a template is made for this replica of master model, a poly-dimethyl siloxane (PDMS) prepolymer was mixed with a curing agent at a 10:1 weight ratio and poured onto the master template. After the mixture is kept on the hotplate about 95◦C for 50 min, the desired PDMS replica was removed from the master template. This is pierced at the channel inlet and outlet using a punch, and bonded to slide glass using oxygen plasma to form the microfluidic channels.

Here we will take an example of lung cancer. For testing Blood specimens from 60 patients with lung cancer and 37 specimens from healthy person is studied. In the beginning CTCs were far away in 58 specimens (96.7%) with a mean number of

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18.6cells/mL (range of 0–129cells), whereas CTCs were observed in 18 out of the 37 healthy persons with a mean CTC count of only 1.2cells/mL (rangeof0–4 cells). The mean CTC counts of patients were significantly higher compared to that of healthy person.

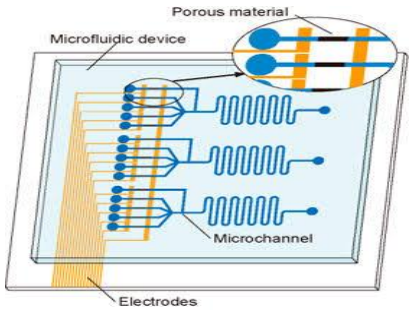

Fig.1 Construction of microfluidic chip

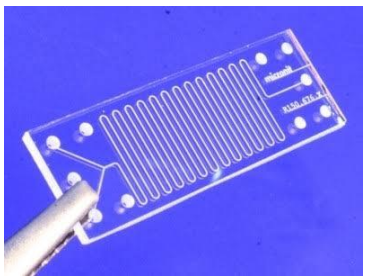

Fig.2 Structure of microfluidic chip

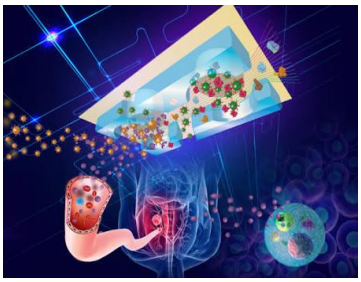

Fig.3 Detection of cancer by using Microfluidic chip

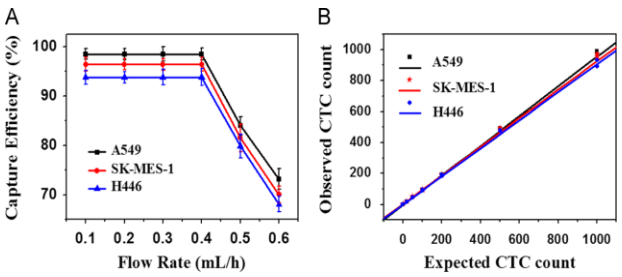

Fig.4 Result of the case study

The optimum cut off level for CTCs to discriminate between healthy persons and lung cancer patients was 5.1 5 cells/ml. This implies that patients with a CTC count of 5.15 cells/mL or more would be diagnosed as lung cancer patients. So this chip provides the significant difference of CTCs between cancer patient and healthy patient. And hence it does not give us any negative results. And hence this is the widest and promising platform for detecting the CTCs.

3. Results and discussion

The sample solution and cancer cells was injected into the inlet of the chip. Its flow is monitored. Cell moves towards the wall because of this flow. If cell is smaller than it will not trap in the filter. Hence efficiency reduces if there are small sized cells. As we studied with various flow rates (0.5–1.5 ml/h), the flow rate doesn't change significantly. We observed that when the flow rate was less than 0.5 ml/h cells trapped in device, whereas many cells were destroyed at flow rates greater than 1.5 ml/hr. If filter gap is decreased from 16 to 10 μm then capturing efficiency increases to 90% also it depends on the width of the filter channel. When the distance between the individual filter channels was greater than 100 μm, the flow rate increases and the cells did not go into the filter gap.

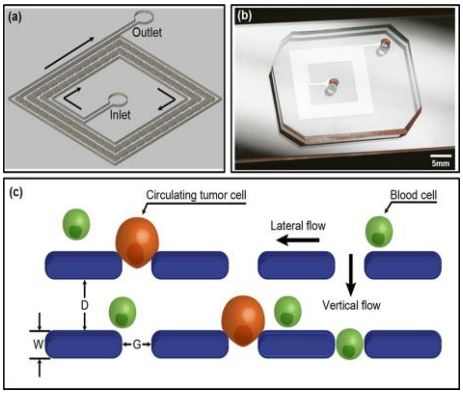

Fig.2 Working of microfluidic chip

Conclusion

1) Microfluidic chip is highly acceptable and precised Technology for the detection of CTCs.
2) It could provide a most useful tool for cancer diagnosis and also it has great efficiency than any other method.
3) As compared to traditional methods such as radiography (X-ray), magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound and some label free techniques it is the best platform to detect CTCs gently from the bloodstream.

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