RESEARCH HIGHLIGHTS

MICROFLUIDICS

Microfluidics and a garden hose

Microfluidics devices are well known for their ability to perform complex manipulations on minute samples, but they can also be powerful tools for analyzing large sample volumes.

Conventional wisdom holds that microfluidic devices are best suited for analysis of minute samples. This has, in fact, been one of the strong selling points that developers and users point to when promoting the technology. Now, in a rather counterintuitive development, Mehmet Toner and coworkers from Massachusetts General Hospital and Harvard Medical School hook their microfluidic chip to a metaphorical garden hose and show that it provides a unique advantage in the analysis of large samples. Their methodology allowed them to settle a longstanding question in the area of cancer biology.

Since the mid-1800s scientists have known that cells from tumors are present in the bloodstream, but nobody has been able to reliably isolate them in large numbers or in all patients. Most believed this reflected the biology and did not consider that the methodology used to find circulating tumor cells (CTCs) was the problem. “Off-the-shelf techniques were used for a very challenging goal,” says Toner. “I didn’t believe the cells weren’t there all the time so we went back to square one with the methodology.”

As would be expected, the multiple processing steps used in existing techniques decrease the efficiency and reliability of the methods, making it very difficult to find rare cells like CTCs. This is particularly true if you need to analyze a whole tube of blood with about 80 billion cells, of which a few hundred may be CTCs. Toner and colleagues thought that a microfluidic device could eliminate the multiple steps and provide very uniform and gentle conditions that would facilitate isolation of rare cells in a large sample of blood.

As a basis for their microfluidic design (Fig. 1), they reasoned that a device composed of thousands of posts for the blood to flow around would provide multiple opportunities for cells to contact the posts. By coating the posts with antibodies to a cell surface protein expressed only on CTCs these rare cells could be retained in the device while unwanted blood cells and plasma flowed through.

Using theoretical modeling they determined that a design consisting of about

Figure 1 | Microfluidic platform used for the isolation of rare circulating tumor cells from a large volume of unprocessed blood.

80,000 posts arranged in a particular alternating pattern would provide a uniform and gentle flow through the device with lower-than-physiological shear stress and enough redundancy to ensure that every cell contacted multiple posts. Toner says, “There is no processing or prelabeled. It is one step from the vacutainer directly through the chip.”

They used their new microfluidic chip to analyze blood from cancer patients and found CTCs virtually all the time, supporting Toner’s original conjecture. “We find CTCs in numbers that are about 100- to 1,000-fold higher than the literature, and the purity of capture is about 50%,” remarks Toner. Even more interesting, they found that when the patients responded to anti-tumor treatment, the number of CTCs went down, and when the tumor volume went up, the CTC number went up. Toner says, “It is essentially a tumor load measurement from a blood test.”

Currently the cells remain in the device after isolation and can be characterized by immunohistochemistry or cell lysis and recovery of nucleic acids. “We are working on ways to make the linkage reversible to release the cells and culture them,” says Toner. “That is one of our major technical goals.”

Toner concludes by saying: “Now we have a very exciting opportunity to have access to the cells that end up killing the patients. I think it is going to open up all kinds of basic studies on metastasis, and the biology and genomics of it.”

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Nagrath, S. *et al.* Isolation of rare circulating tumour cells in cancer patients by microchip technology. *Nature* **450**, 1235–1239 (2007).