Tracking CTCs May Improve Cancer Treatment

Technologies that find and characterize tumor cells in blood could aid in disease management

At some point in their growth, solid tumors begin to shed cells into the bloodstream. There is growing interest in using these rare circulating cells, commonly called circulating tumor cells (CTC), as a liquid biopsy, allowing doctors to determine the course of therapy, watch how a patient's cancer evolves, and follow patients in remission—all with a blood draw.

CTCs were first observed in 1868, but it wasn't until 2004 that researchers published the first evidence, in breast cancer, that CTC counts have prognostic value. Since then, the presence and number of these cells in blood has been associated with disease progression in patients with prostate and colorectal cancer, yet clinicians rarely order these tests. In part, this is because CTC counts cannot yet be used to routinely guide therapy.

Researchers aim to change that by putting more powerful CTC technologies to the test in clinical studies. Beyond counting CTCs, they want to more thoroughly characterize them—whether by looking for protein markers or single gene expression patterns or, in the future, by sequencing their genomes. This information should provide insights into cancer biology and make CTC tests clinically useful.

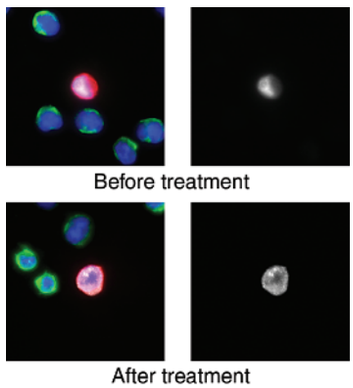
CAPTURING CTCs

The only FDA-approved method to capture CTCs is CellSearch, marketed by Janssen Diagnostics of Beerse, Belgium. It uses magnetic particles decorated with antibodies against the epithelial-cell marker EpCAM and subsequent staining for CD45 and cytokeratins to capture and identify CTCs.

However, researchers believe CellSearch misses many CTCs, says Daniel Haber, MD, PhD, director of the Massachusetts General Hospital Cancer Center and professor of oncology at Harvard Medical School in Boston. These systems find only what they have been designed to look for, and the understanding of cancer biology and metastasis has evolved since CellSearch was considered state of the art. In addition, many CTCs lack EpCAM and other epithelial markers. Those that look less epithelial, in fact, may be more clinically relevant: In breast cancer, for example, such CTCs have been linked to chemoresistance and metastasis.

In the last few years, approaches for more effectively capturing CTCs have proliferated, most designed to exclude fewer tumor cells. There are currently some 50 competing technologies, estimates Klaus Pantel, MD, PhD, chair of the Institute of Tumor Biology at the University Medical Center Hamburg-Eppendorf in Germany. These new technologies are enabled by developments in microfluidics for sorting cells and new microscopy methods. Some filter cells by size or physical properties, such as how they move through fluid, while some rely on surface chemistry and imaging. Others use multiple methods.

Researchers also want to go from counting cells to characterizing them, and from estimating survival to choosing personalized therapies. "We need to determine how best to use CTCs to help with clinical decisions, especially as new therapies are developed," says Stefanie Jeffrey, MD, chief of surgical oncology research at the Stanford University School of Medicine in Palo Alto, CA.



These images show CTCs in a patient with prostate cancer, with normal white blood cells in blue and green and cancer cells in pink, blue, and white. White represents androgen receptors (AR), which can be seen more clearly in the right images. With antiandrogen treatment, the ARs move from the nucleus to the cytoplasm, a sign that the tumor is responding to the drug.

The value of CTCs in guiding therapy is now being tested. For example, researchers at the Institut Curie in Paris, France, are comparing outcomes in hormone receptor–positive breast cancer patients who were treated more or less aggressively based on either CTC counts or the clinician's discretion.

Other trials aim to understand tumor biology through CTCs. Breast cancer patients with HER2-negative tumors are not treated with HER2-targeting therapies such as lapatinib (Tykerb; GlaxoSmithKline). Surprisingly, though, some of these patients have HER2-positive CTCs. In DETECT III, a phase III trial under way in Germany, researchers are assessing whether lapatinib might be effective in these patients.

One promising new technology currently in clinical trials, being developed by Epic Sciences of La Jolla, CA, uses a large number of imaging labels to spot more CTCs and provide information about them, says Peter Kuhn, PhD, a professor of cell biology at La Jolla's Scripps Research Institute, who developed the technology. This is critical because CTCs are relatively rare: Only one out of every 1 million to 100 million cells in a cancer patient's blood is a cancer cell. The system uses software that picks out tumor cells and looks for markers that might suggest how aggressive they are and what drug sensitivity the patient's tumor might have.

One Epic Sciences study involves prostate cancer. Patients whose tumors have lost *PTEN* might do better on a therapy that targets the PI3K/AKT pathway. Epic Sciences wants to look for this with a blood test, rather than by using a traditional biopsy. In 2013, researchers showed that CTCs from prostate cancer patients could be used to determine *PTEN* status using fluorescence *in situ* hybridization to look for the gene in cells captured by the Epic technology. The technology is also being tested in 24 observational clinical trials in breast, lung, pancreatic, and ovarian cancers, among others.

"We're moving from enumeration to characterization of these cells," says Jeffrey. "The key is relating this to how to choose therapies." ■

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