Proteomics delivers on promise of cancer biomarkers

Hot on the trail of cancer biomarkers—telltale proteins in body fluids that can expose a malignant tumor—researchers are using the latest in proteomics techniques. Many groups have taken tracking to a new level, seeking proteins in specific fluids or tissues, searching for wayward, circulating cancer cells or using pattern-recognition software as an early-warning system for specific tumors.

Some cancers already have specific biomarkers, such as prostate-specific antigen for prostate cancer, or accurate diagnostic tests such as colonoscopy for colon cancer. But none exist for two big killers: breast and ovarian cancer. An early-detection biomarker could catch breast and ovarian cancers as early as stage I, when patients have at least a 90% chance of survival, experts say. Most of those tumors are now diagnosed at later stages, when survival rates drop to 15–35%.

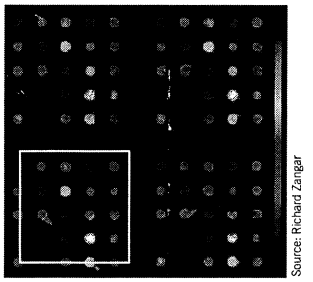
Until recently, researchers had been looking for a single biomarker in blood serum. But serum is a complex, ever-changing source of proteins, and a marker found there cannot easily be traced to organs. These obstacles have prompted scientists to brew unusual solutions.

A clinical proteomics program jointly run by the US National Cancer Institute (NCI) and the US Food and Drug Administration (FDA) created a stir last year when its researchers developed a diagnostic test that is 100% sensitive (catching all instances of ovarian cancer) and 95% specific (yielding 3 false positives out of 66 healthy women). Rather than look for a specific protein, the group analyzed blood samples for multiple protein markers and found a 'cancer signature'.

"What others might consider to be a garbage dump of protein fragments shed into the circulation, we think is a gold mine of information," says NCI researcher Lance Liotta, codirector of the program. The team has now increased specificity to 100% by boosting the mass spectrometer's resolution and feeding more data into the model.

But Emanuel Petricoin, codirector of the program at the FDA, warns that no test can ever be 100% accurate. The real proof of the method, he says, will be how it fares in the FDA clinical trial, scheduled to begin in a few months.

"Despite the promising data, there are skeptics," notes Eleftherios Diamandis, a pathologist at the University of Toronto. Diamandis suggests that the technique picks up the body's systemic responses to cancer, not signals from the tumor itself. He places more faith in protein microarrays, in which antibodies capture protein profiles of various tumors.



Source: Richard Zangar

Chips ahoy: An ELISA microarray analysis of a serum sample taken from a woman with breast cancer. Twenty-one separate assays, each replicated four times, are performed on a single chip.

Researchers at the Pacific Northwest National Laboratory in Washington have developed one such protein array based on breast-specific nipple aspirate fluid (NAF). Because NAF is secreted from ductal cells, the source of nearly 80% of all breast cancers, "it is likely to be an ideal source of breast cancer markers," says Richard Zangar, the lead investigator.

The team's analysis of NAF from healthy women turned up 15 biomarker candidates with known roles in cancer, including cathepsin D and osteopontin, which are elevated in the serum and tumor tissue of breast cancer patients.

Other teams are using a functional approach to uncover beacons of the earliest stages of cancer. For instance, Zangar notes, some of the NAF proteins are cell-surface proteins that are shed, or released, by proteases. This process is disrupted in tumor cells but, through cell-to-cell signaling, is amplified in the surrounding normal cells. Tracking the shedding of protein fragments might allow researchers to detect the effects of just a few early tumor cells.

Another group, led by Joshua LaBaer, director of the Harvard Institute of Proteomics, is helping scientists screen the function of the top 1,000 genes related to breast cancer; 500 genes have already been cloned. To generate the list of 1,000, the researchers developed a software tool called MedGene that trolled through publications for gene names tightly associated with breast cancer. They actually found 2,400, which underscores the complexities these protein hunters face, LaBaer says. "Anything that plays a role and leads us to answers about how the disease starts could be a biomarker."

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