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NEWS

Comparing Microarray Data: What Technology Is Needed?

Tom Hollon

DNA microarray analysis is gaining popularity and revealing gene expression patterns that accompany major cancers. The amount of information that can be revealed by a single microarray, a powerful tool that can simultaneously analyze changes in the structure or expression of thousands of genes, is impressive and, at times, overwhelming.

As the technology progresses, researchers will inevitably want to compare data from microarray experiments conducted by different laboratories, hoping that a deeper understanding of cancer will emerge. One of the many uses for microarray analysis is to develop gene- and protein-based classification systems for different cancers. This "molecular taxonomy of cancer," as [Jeff Green](#), M.D., director of the National Cancer Institute's Advanced Technology Center, put it, will supplement standard cancer histopathology and may improve diagnosis and treatment as more is learned about cancer subtypes and as more molecularly targeted therapies are developed.

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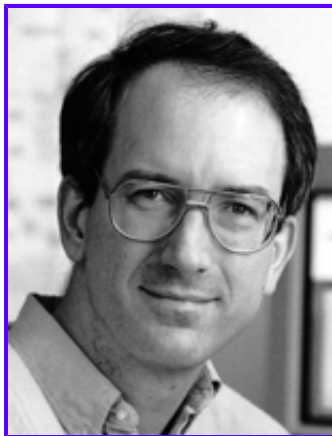
**Dr. Jeff Green**

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But numerous differences in how microarrays are created and used, and how data are analyzed, make quantitative comparisons "very tricky," said [Louis Staudt](#), M.D, Ph.D., of the NCI's Center for Cancer Research. Quantitative comparison of gene expression levels measured with different microarrays requires proper software and a common standard for comparing measurements. Without those essentials, it is an exercise to be avoided. So what will it take to make cross-microarray comparisons possible?

**Dr. Louis Staudt**

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Researchers at NCI have started to solve the problem by acknowledging why microarray data can be different from one chip to the next.

To begin with, commercially available chips, which are very popular, have two different hybridization substrates, oligonucleotides and cDNAs. Some scientists have had trouble obtaining similar results with the two formats, although if used correctly, they should be comparable, said Staudt.

There are also many specialty chips created by academic researchers wanting to study genes not available on commercial chips. Data obtained with these specialty microarrays might be difficult to compare because of different spotting methods, DNA concentrations, and clone purity. Laboratories also obtain different results because of different methods of preparing mRNA used to make hybridization probes, and different hybridization conditions.

A way to correct for many of these differences may be to include reference RNA as a hybridization control when doing an experiment, said NCI's Green. With the use of reference RNA, each spot on a chip can have two gene expression measurements, one representing gene expression in the experimental sample and the other a baseline measurement representing expression in the reference RNA.

Hybridization probes derived from experimental and reference mRNA are mixed together and hybridized at the same time, experimental probes labeled with one color, reference probes with another. If different microarrays use the same reference RNA, said Green, quantitative gene expression comparisons across microarrays should be possible.

Suppose, for example, that for one microarray a particular gene's expression is fivefold higher than its reference baseline, and for another microarray for a different cancer, it is 20-fold higher. "We can conclude that between the two experiments, the gene is expressed four times as much in one as the other," said Green. Again, such knowledge has implications for understanding cancer subtypes and treating them with targeted drugs.

Testing Reference RNA

Green and his colleagues are in the early stages of testing a commercially available reference RNA made from 11 different cell lines representing several types of tissues. If this standard proves suitable, it will be available in large quantities for laboratories in the NCI

program, so investigators within the program can use the same reference standard in each of their experiments. Their data should be quantitatively comparable.

But reference RNA from cell lines will not be a total solution, said Lothar Hennighausen, Ph.D., chief of the Laboratory of Genetics and Physiology at the National Institute of Diabetes and Digestive and Kidney Diseases, who is studying gene expression in normal and neoplastic mammary tissues of mice. Hennighausen noted that mRNA from cell lines does not represent every gene expressed *in vivo*. Some genes in mammary glands, he observed, are never expressed in cell lines. "So you may want in addition a standard reference RNA from normal tissue."

One of Hennighausen's goals is to learn how closely several mouse models of breast cancer resemble the human disease. After 2 years of working with microarrays that were suboptimal to his needs, he is waiting on delivery of chips representing most of the genes expressed in mouse mammary tissue. He and a group of collaborators will use the chips as a common standard and plan to make quantitative comparisons of their data.

Solid Tumor Complexity

A particular problem they face is the complexity of cell types in a solid tumor. To deal with this, "eventually you probably have to do *in situ* hybridization assays to identify the respective cell types." In contrast, he pointed out that rapid progress can be made with microarray studies in tissue culture cells, and leukemias and lymphomas, Staudt's field, "because there you have more homogeneous cell populations," he said. "You get a much cleaner signal."

Indispensable to quantitative data comparison is proper software. Hennighausen and his collaborators use a program called MicroArray Explorer, developed by computer scientist Peter Lemkin, Ph.D., of the NCI's Laboratory of Experimental and Computational Biology. MicroArray Explorer makes it possible to analyze quantitative cDNA expression profiles across multiple microarrays. This has been used to analyze gene expression patterns for over 1,500 genes isolated from mouse mammary tissue. The software in fact was originally designed for Hennighausen's project. "The idea," said Lemkin, "was that the arrays would be distributed to different groups, who would then build one big database."

Staudt is doing his part to make cross-array comparisons easier by sharing his data. His

"lymphochip" microarrays have revealed gene expression patterns that distinguish new B-cell lymphoma subtypes. Staudt's Web site, where his microarray data are freely available, contains a list of B-cell lymphoma genes regulated by IL-2. Someone conducting microarray experiments with T-cell lymphomas would find that list of great value, he said.

"This would be the indirect retrieval of information from one experiment and its use to interpret another," he said.

Staudt added that investigators can make their microarray data more amenable to qualitative comparison by "summarizing the take-home lessons" from their experiments. Identifying groups of genes that define the biology studied would be particularly helpful. Other researchers could then apply that information to their own experiments, he said.

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