DNA chips hold great disease fighting potential

By DEBBIE BEREBICHEZ

The background on DNA microarrays

In the 1950s scientists discovered that the molecule of DNA carried the genetic information that characterizes our traits and differentiates us from even our closest relatives. The work of Crick, Watson, Franklin and Wilkins established the shape of the molecule as two strands that wrap around each other, resembling a twisted ladder whose sides, made of sugar and phosphate molecules, are connected by rungs of chemicals called bases. Four different bases are present in DNA: adenine, thymine, cytosine and guanine.

It was later found that DNA in the cell produces RNA, and that RNA in turn translates into proteins. The messenger RNA transfers the gene's instructions, thus prescribing the creation of proteins by ribosomes. Is is interesting to note that not all the genetic code in DNA gets translated into proteins; only certain genes are expressed. Different genes get expressed in different quantities at different times. Hence, it is essential that the cell is careful in carrying out the regulation and control of this expression.

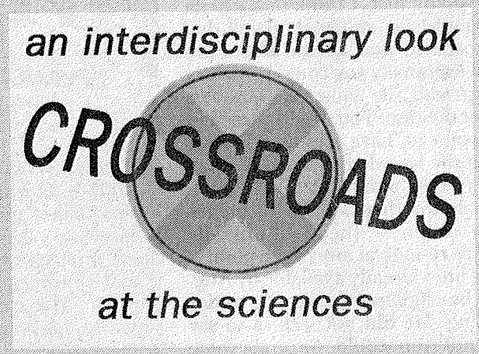
What factors cause cancer?

Environmental toxins, free radicals, viruses and radiation can all damge the DNA in a cell. When a cell is damaged, the pattern of regulaton of its original gene-expression levels gets distorted. This distortion may cause a cell to become cancerous. Generally, it is clusters of genes that, when affected, develop into cancer. A cancerous cell will exhibit different patterns of gene regulation than will a healthy, normal cell.

What are DNA microarrays?

DNA microarray technology was pioneered by Genetics Prof. David Botstein and Biochemistry Prof. Patrick Brown, both professors at Stanford. This novel technique may be used to easily detect cancer in human cells. DNA microarrays are essentially glass slides covered by DNA, that enable researchers to analyze the whole genome on a single chip. For his work with DNA microarrays, Time magazine named Brown as one of "America's Best" scientists in the field of genetics.

"A DNA microarray can be used as a new kind of microscope that allows us to observe a genome's gene expression program," Brown said. "Each cell in our bodies expresses a specific set of genes according to a precisely controlled genetic script that gives that cell its distinctive design and functional capabilities. The gene expression program that unfolds during developmental or physiological process can be read as a kind of script for that process."



How do DNA microarrays work?

DNA microarrays, also known as DNA chips, rely on the process of DNA hybridization, in which DNA bases pair up wth their RNA base counterparts. DNA chip technology works by placing different DNA samples on a glass microscope slide in a highly dense grid. The slide is exposed to labeled DNA, or a complementary DNA copy of messenger RNA, which hybridizes with the DNA on the glass slide. Finally, researchers analyze the amount of hybridization in each spot on the slide.

The genes that hybridize the most are the most active genes, and those that hybridize the least are repressed genes. Depending on the amount of hybridization, the genes are tinged with a certain color, with more expressed genes appearing in redder shades, and more repressed genes appearing in greener shades. This helps researchers judge with genes are activated in a healthy cell and which are activated in a cancerous cell.

Using DNA microarrays to predict cancer occurrence

Recent progress in understanding the molecular basis of cancer has shifted the focus of its early detection from identifying the physical presence of a tumor to detecting the unique moleular signatures indicative of its presence. DNA microarray technology promises great success in human diagnostics for detecting modifications in gene expression within specific cell or tissue types. It also proves useful in distinguishing physiological states and genetic makeup of the patient by determining which genes are active and which ones are repressed when different populations of cells are compared.

Scientists can investigate a patient's sample to try to find changes in gene expression that may be indicative of an unhealty state or cancerous growth. The important lead is that gene-expression patterns are distorted when defective genes give rise to the uncontrolled division of cells. It is these patterns that may help scientists understand precisely what is wrong in a cell, or, at the very least, help identify a tumor.

In contrast to conventional cancer screening tests, DNA chips offer a novel approach in that they allow researchers "to search for subgroups of a variety of types of cancers," Prof. Botstein said.

Another advantage of microarray technology is its vast processing power. The technique can perform huge batteries of tests that once tooks weeks in a fraction of the time.

"We use DNA microarrays containing up to 30,000 different human genes to survery the gene expression patterns in thousands of samples of human cells and tissues under diverse conditions," Prof Brown said. "These studies are providing detailed molcular pictures of the programmed responses of the human genome to diverse physiological and pathological conditions, and they are yielding clues to the mechanisms by which these processes are deranged in cancer and other disease processes.

Cancer studies with DNA chips

An application of the DNA microarray method is to compare the genes in healthy versus cancerous breast tissue and at various stages of breast cancer progression. Mike Wigler and Larry Norton of the Cold Spring Harbor Laboratory and the Memorial Sloan-Kettering Cancer Center, respectively, are using DNA chip technology for this purpose.

Todd Golub and 11 colleagues at Harvard Medical School reported in Science magazine about their use of DNA chips to distinguish between two forms of leukemia. The cancers detected for this trial run were previously distinguishable using conventional methods, but this trial was a valuable opportunity to test the accuracy of DNA microarray technology.

An article in The Scientist magazine reported the results of the leukemia study.

"Applying a 6,817-gene chip to 38 bone marrow samples, the investigators identified 50 genes whose expression most distinguished acute myeloid leukemia from lymphobladtic leukemia," said the article. 34 samples drawn from a wider range of sources were then analyzed. Expression patterns, determined with DNA chips, accurately predicted the type of leukemia for 29 of the 34 samples."

These results were clinically significant because the two types of leukemia require very distinct treatments. Golub and his colleagues are now employing DNA chips to investigate cancers of the brain, prostate and lung.