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Genomics Part II: DNA Microarrays

Genomics can be defined as the study of the entire compliment of genetic material, or all the genes, of an organism. This can encompass studying how genes work together, how different genes affect one another, and how the same gene differs in small ways between individuals.

Genome sequencing can be thought of as learning the language of the genes in an organism. The amount of information churned out in a sequencing project is enormous, and in many cases a lot of work remains to make sense of the sequence before study of the genes encoded can even begin. Today we are witnessing the technological breakthrough that may make it possible to study every gene in an organism at once – it's called a DNA microarray.

Array of hope

A DNA microarray, or DNA chip, represents the convergence of two scientific disciplines that once seemed very different: molecular genetics and computer science. Based on the technology developed in the early 1960s in the circuitry field, a DNA chip is composed of a glass or silicon surface studded with DNA fragments, and is smaller than a postage stamp. This array of DNA allows researchers to study many genes at once in a single quick test. This is important because we could spend forever studying each gene in turn and never appreciate how they all work together to make tissues and cells function.

Nanogen's NanoChip™ handheld DNA chip and sample-handler; the sample ports are at the top, and the chip is the diamond in the centre.

A chip off the old block

The DNA microarray, or DNA chip as it is sometimes called, is built on concepts learned over years of research in biology and genetics. What is remarkable is that fifty years ago, scientists had no idea what DNA even looked like. It was 1865 when an Austrian monk named Gregor Mendel published a study showing how living things – pea plants in his garden, to be exact – inherit physical characteristics. It was not until 1953 that James Watson and Francis Crick elucidated the structure of DNA. In 1959, in the unrelated field of computer electronics, the first integrated circuits were built, beginning the trend toward miniaturization in computers. Decades later, the process developed to build these circuits, called photolithography, would be adapted by molecular biologists to build DNA chips.

The final piece of the puzzle that would be necessary for the idea of DNA microarrays to evolve was the concept that single stranded DNA attached to a solid support could be used as "bait" to attract complementary strands. This idea was first proposed in 1965, and in 1975 biologist Ed Southern popularized a method for cutting DNA in manageable units and securing these fragments to a piece of filter paper for analysis. This method, called Southern blotting, is the predecessor to the DNA microarray. Scientists at a California-based biotech company called Affymax would produce the first DNA chips in 1991.

Complementarity is the key

A DNA microarray works because of a fundamental aspect of the structure of DNA. DNA is a double stranded molecule, twisted like a telephone cord. Each strand is composed of a series of nucleotide bases, and each of the four bases (A, T, C, and G) has a partner. A always partners with T, and C always partners with G. This means that the sequence AATTCGCT will always have a partner, or complementary, strand having the sequence TTAAGCGA.

Complementary base pairing is the basis of DNA replication. The two strands of a DNA molecule can "unzip", and new daughter strands can be built using each parent strand as a template. We can force a double stranded DNA molecule to unzip to form two single strands by applying heat. The unzipped single strands will then be available to bond to a partner strand with a complementary sequence. This is the basis of how a DNA microarray works.

Single stranded DNA is bound to the surface of the microarray. Different genes or sequences are tethered at different points in the array, and the researcher knows what the sequence is at each point. A solution containing unknown sequences of DNA labeled with fluorescent molecular flags is then sloshed over the surface of the microarray, and if any of the unknown DNA finds a complementary partner sequence in the array, it will bind to it. Unbound DNA is then washed off the surface. By looking at where the fluorescent flags are stuck to the microarray, the scientist knows where the unknown sample bonded, and because the sequence of the DNA used as "bait" is known, the sequence of the unknown sample can be deduced.

An array of applications

DNA chips are currently being used in a field of study called functional genomics. Scientists use microarrays to observe genes working together in a process called "expression analysis". In this type of study, the DNA used to create the microarray is often from a group of related genes such as those expressed in a particular tissue, during a certain developmental stage, or after treatment with a particular drug. Using a microarray, scientists can observe how these genes interact with one another and with the cellular environment.

Another way DNA chips can be used is to map the differences between individuals. If you select any two people in the world, their DNA would be 99.9 percent identical. The remaining 0.1 percent is the genetic basis for all of humanity's differences, from different eye or face shapes, to different skin colors, to the way different people respond to medical treatment. These tiny differences in DNA sequence are called "single nucleotide polymorphisms" or SNPs. Identifying them could help us develop treatments customized for individual people and illnesses, and identify people prone to illnesses such as some forms of cancer, diabetes, and Alzheimer's before they become ill.

Today DNA microarrays are tools that help scientists make sense of the vast amount of information flowing out of genomics projects around the world. Tomorrow you could see them showing up in everyday life; in the doctor's office where they'll help your doctor determine whether you'll react well or poorly to a drug, or what kind of bug you've caught; or even in a police detective's toolkit where they'll help convict the guilty and clear the innocent.

For more information:

University of Washington: http://w.cs.washington.edu/homes/jbuhler/research/array/

FLASH animation of microarray methodology: http://www.bio.davidson.edu/courses/genomics/chip/chip.html

Snapshots online magazine for high school teachers: http://science-education.nih.gov/newsnapshots/index.html

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