Microarray Technology in Pathology*

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Abstract

Microarrays are a promising new technology in medicine. Microarrays offer a powerful new diagnostic technique that will revolutionize clinical medicine.

Introduction

The microarray is a powerful new method which will significantly advance clinical medicine as we know it. Pathologists should be educated on the use of microarrays in a clinical setting. As the technology is steadily developed, it will continue to grow and gain precedence.

Potential

Microarrays may be used for gene expression profiling, genotyping, mutation detection, and gene discovery[1]. Expression profiling underlies microarray technology. Essentially, a microarray is very similar to a Northern blot, but the extent to which it simultaneously analyzes multiple genes from a single sample (its capacity) is extraordinary. In gene expression profiling, cellular RNA, which has been labeled with a fluorescent marker, is hybridized to a biochip (microarray). Gene expression profiling may be used to differentiate kinds of cancer with varying prognoses, or to identify different strains of a pathogenic organism, which may or may not respond to certain antibiotic treatment. In genotyping, the genomic DNA is amplified with PCR, and hybridized to specific sequences on the biochip. Genotyping may allow one to predict a patients risk of developing a certain disease by determining the presence of genetic markers. Genotyping may also be used in pharmacogenomics, to determine if a patient will have an adverse reaction to a drug or if the drug will be effective.

Techniques

Types

There are two basic types of microarrays: the spotted microarray and the photolithographic microarray. Spotted microarrays contain DNA that has been adhered to, or spotted on, a glass slide. A spotted microarray is also called a complimentary DNA microarray. Photolithographic microarrays contain oligonucleotides that have been synthesized on a silica slide by photolithography. Photolithographic microarrays have a higher density of spots, i.e. more genes per unit area. A photolithographic biochip is also called an oligonucleotide microarray. Microarray sequences may come from cDNA, ESTs, or other sources.

Analytical Methods

Microarray data may be analyzed with a supervised or unsupervised method. Supervision refers to the fact that one is demanding that data fit a given pattern. Supervised techniques include nearest neighbors and support vector machines. Unsuper-

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vised techniques include hierarchical clustering, self-organizing maps, relevance networks, and principal component analysis[2].

Measures

No two individual biochips will have a similar amount of fluorescence; not even two biochips from the same sample. This happens because the conditions under which each microarray is made are not exactly reproducible. Therefore, the results need to be normalized. In addition, a certain amount of biological noise, technical noise, and heterogeneity must be factored out. Despite what has been said, spotted cDNA microarrays and oligonucleotide microarrays are not directly comparable owing to the irreconcilable difference in their methods of preparation.

Dissimilarity measures are used in all of the analytical methods. Four dissimilarity measures are as follows: Euclidean distance, Pearson correlation coefficient, rank correlation coefficient, and mutual information[2].

Problems

Most of the concerns about microarrays are attributable to the fact that it is a new technology. Because it is a new technology, there are no established procedures or regulations to validate different approaches to its use. No well excepted standard exists, and many question the validity of various data gained from microarray analysis. An example is the arbitrary selection of genes to be analyzed on a specific biochip. Even the preparation of a biochip has not been standardized, though widely available commercial preformed biochips may reduce the concern to preparation of extracts in some instances.

Another concern in using microarray technology is the accuracy of computations. A formula, such as a metric, may be controversial. Differing equipment and software will most likely produce differing results when analyzing the intensity of fluorescence in biochip spots.

Examples

A basic science example of classifying gene function with biochips is given in Kluger et al. Here, they identified genes involved in tumor formation in a breast cancer model. Mouse mammary epithelial cells were transfected with a wild type oncogenic receptor and receptor mutants. The wild type mutation was matrix-independent, metastasizing, and invasive. Depending on the receptor (tyrosine) kinase location that was mutated, the transfected cells lost either matrix-independence/metastasis or invasiveness. Through cluster analysis of gene expression, using microarrays, they were able to identify possible genes involved in matrix-independence/metastasis and invasiveness in the breast cancer model. Unknown genes, to which the ESTs (expressed sequence tags) were available were also implicated; this is a further step in revealing the function of these unknown genes.

Conclusion

Microarray technology must be developed further, but it has proven to be the next generation of diagnostic technology. Through expression profiling, we may make pharmacogenomic predictions, prognoses for similar diseases, assess the pathogenecity of an organism, and do much more.

References

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