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APPLICATIONS OF THE DNA MICROARRAY TECHNIQUE

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Abstract: The completion of the sequencing of the human genome in 2001 has made it possible to carry out numerous experiments and research. Research methods are evolving from traditional molecular biology methods to methods in which multiple genes can be analyzed in a single experiment. Microarray technology can achieve the screening of thousands of DNA and protein samples simultaneously. The basic principle of microarrays is hybridization between two DNA strands. This method is widely used in various fields: genomics, proteomics, personalized medicine, vaccine screening, toxin screening, post-translational modifications, molecular diagnostics and drug discovery. In this review, the basic principles of gene expression microarrays, the types and potential applications of this technique are detailed.

Keywords: DNA microarray; drug; cancer; genetic polymorphism

Introduction

The completion of genome sequencing of many organisms has led to the evolution of research from sequencing to identifying the genes of a particular organism and their biological functions. Research methods have evolved from traditional molecular biology methods to methods in which multiple genes can be analyzed in a single experiment. The microarray technique was first used for immunological tests. But, today, different types of microarrays (DNA, proteins, tissues) can be powerful and sensitive tools for analyzing thousands of molecules in a biological system, leading to a global picture of the system under study (Howbrook et al., 2003; Templin et al., 2002).

Thus, in recent years, microarray technology has become a technology of interest in biological research, because through miniaturization, it allows the analysis and monitoring of numerous genes on a single chip, and through bioanalytical detection, it allows obtaining information about the interactions between thousands of genes simultaneously. Thus, numerous molecules can be detected simultaneously in a single experiment, using a small amount of sample, but also with high sensitivity (Howbrook et al., 2003; Templin et al., 2002; Shi et al., 2003).

Microarray technology is a valuable tool in genomic research, representing a rapid and efficient method for analyzing gene expression. Knowledge of rapid quality monitoring techniques, such as microarray technology, as well as their use and implementation, makes it possible to identify and resolve potential

problems more quickly, thus achieving the safety and efficacy of pharmaceutical products (Howbrook et al., 2003).

The aim of this paper is to identify the benefits and limitations of microarray technology, thus highlighting the utility and accessibility of this technique in the future.

DNA microarray technique – description and classification

A microarray (DNA chip or biochip) experiment involves the hybridization of an mRNA molecule to the DNA template from which it originates. The amount of mRNA bound to each site on the array indicates the expression level of the various genes. The data is collected by the system, which generates a gene expression profile. Thus, in the DNA microarray technique, numerous single-stranded DNA molecules are attached and immobilized to a solid nylon or glass surface of the chip. The samples can be represented by cDNA sequences (complementary DNA) amplified by PCR or by short DNA oligonucleotide sequences (Shin et al., 2005; Leveque et al., 2013; Chiodi et al., 2021).

Regarding the operating principle of the microarray technique, it can be schematically represented by: 1. Sample Preparation: extraction of RNA or DNA from cells of interest; reverse transcription of RNA into complementary DNA (cDNA) if necessary, using the enzyme reverse transcriptase and fluorescent labelling of DNA or cDNA samples to allow detection. 2. Hybridization: incubation of the labeled sample with the chip, where hybridization of the sample with single-stranded complementary probes fixed to the chip occurs; based on complementarity, only sequences in the sample that are complementary to the sequences on the chip will bind. 3. Washing: removal of sequences that are not specifically bound to the chip; only strongly bound sequences remain hybridized to the chip. 4. Scanning: scanning the chip to detect fluorescent signals. 5. Data analysis: visualization of the fluorescent signal intensity to determine gene expression levels and use of specialized software for data analysis (Shin et al., 2005; Leveque et al., 2013).

The basic principle of microarrays is hybridization between two DNA strands, which refers to the ability of complementary nucleic acid sequences to interact and bind specifically, by forming hydrogen bonds between complementary nitrogenous base pairs. The intensity of the fluorescent signal of the labeled target sequences depends on the strength of the hybridization and is determined by several factors: the number of complementary base pairs, the hybridization temperature, and the post-hybridization wash. The signal of a spot depends on the amount of target sample that binds to the probes present in that spot. This technique uses relative quantification, in which the intensity of a feature is compared to the intensity of the same feature under a different condition (Drmanac et al., 1998; Pollack et al., 1999; Ma and Horiuchi, 2006).

The main types of microarray technologies can be classified as in **figure 1**. (Baldi and Hatfield, 2002; LaFramboise, 2009; Arenkov et al., 2000; Limberger et al., 2017).

Applications of DNA microarray technology

Applications of microarray technology have been increasingly developed in recent years, showing the superior power of this technology for the massively parallel analysis of biological samples or the identification of genes and their functions or their mutations.

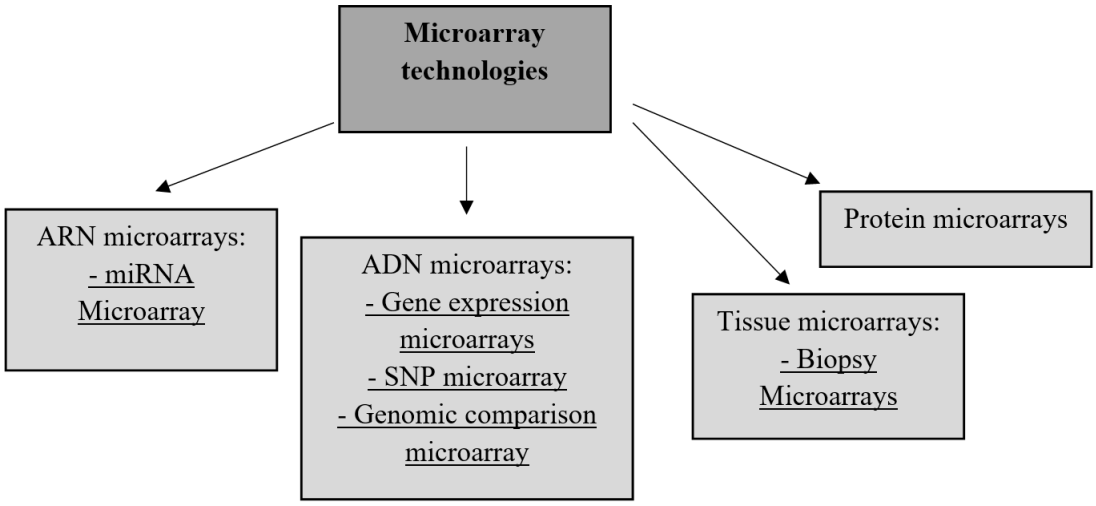

Fig. 1. Classification of the main types of microarray technologies

This method is widely used in various fields, including genomics, proteomics, personalized medicine, screening of vaccine candidates, toxin screening, post-translational modifications, molecular diagnostics, and drug discovery (Miller and Tang, 2009; Aparna and Tetala, 2023).

Drug development

Microarrays play a critical role in the discovery and development of new drugs. They are used to assess the effects of chemical compounds on gene and protein expression, identifying potential drug candidates. Gene expression studies can highlight molecular targets for therapeutic interventions and help understand the mechanisms of action of drugs (Ma and Horiuchi, 2006; Miller and Tang, 2009). To determine the therapeutic efficacy of drugs and their potential for risk, a development process involving testing of their metabolic function and toxicity occurs (Ishida et al., 2018). Some studies have shown that in vitro cell microarrays are successfully used in drug screening studies. They have a short analysis time and low cost, which reduces the need for animal testing studies. With these microarrays, specific analyses can be determined, such as the response to a drug treatment or cell-cell interactions. In addition, these microarrays can be used to determine the toxicity and side effects of pharmaceutical compounds by studying changes in gene expression in response to treatment. This allows the identification of potential safety issues at an early stage of drug development and reduces the risk of failure in later stages (Miller and Tang, 2009).

The interaction between different cell types can be understood using three-dimensional (3D) cell microarrays that can be used as an alternative to conventional two-dimensional (2D) multi-well plate assays (Gurski et al., 2010; Souza et al., 2010). It has been shown that compared to cells from native tissues and those in 3D culture conditions, cells that are cultured in 2D monolayers show significant changes in gene expression. (Gurkan et al., 2010; Pampaloni et al., 2007) Researchers can define structure-function relationships using 3D cell cultures, but they can also allow the observation of cellular events, disease progression, and response to different drugs. Microengineering and specific technologies allow the fabrication of cell-based 3D microarrays, including cell printing and surface patterning (Birgersdotter et al., 2005; Kunz-Schughart et al., 2004).

Cell printing has been shown to produce repeatable and uniform 3D cell aggregates and constructs. However, there are some difficulties with existing cell printing technologies, such as low cell viability and loss of cell functionality. However, acoustic cell printing technologies are now available that offer advantages over existing printing technologies in terms of higher cell viability and functionality (Guillemot et al., 2010; Xu et al., 2008; Jayasinghe et al., 2006).

To print cells on streptavidin-coated slides, Hart et al., (2009) used a robotic microarray placement device, with cells being placed in collagen or alginate nanodroplets. (Hart et al., 2009) Using the robotic system, these can be assembled onto a glass slide to form 3D cell microarrays. Such bioprinting platforms can be used to ensure controlled and high-yield delivery of drugs into cellular matrices. Therefore, bioprinting technology is a suitable method for the formation of 3D cellular matrices, but also for the delivery and testing of compounds (Fernandes et al., 2008; Park et al., 2010).

For successful and high-throughput drug screening, controlled drug delivery into cell microarrays is extremely important. A simple way is to load drugs using a robotic system. However, loading numerous chemicals into cell microarrays can take a long time: hours or even days. Cell viability and reproducibility of cell-drug responses can be affected by the long loading time. To efficiently deliver drugs into cell microarrays and overcome the time barrier, various methods have been developed: drug patterning, microfluidic drug loading, and aerosol sprays (Upadhyaya and Selvaganapathy, 2010; Gosalia and Diamond, 2003; Ma et al., 2005; MacBeath and Schreiber, 2000).

Due to microengineering and advances in the field (microfabrication and soft lithography), it has been possible to fabricate high-density well arrays with well sizes ranging from tens to hundreds of micrometers. In drug design, lithography has become increasingly popular due to its low cost and compatibility with a wide range of materials. The wells are loaded with cells immobilized inside these microwells, forming cell microarrays. They are used in pharmaceutical research for the identification of therapeutic targets and analysis of drug effects, as well as for the development of biomarkers and personalized therapies (Sui et al., 2013; Candela et al., 2010).

Detection and identification of bacteria and viruses

Since thousands of DNA or RNA sequences can be analyzed simultaneously with the help of microarray technology, it makes it a useful technique in microbiological diagnostics, molecular epidemiology and pathogenicity studies. Molecular methods such as PCR, real-time PCR have replaced the laborious traditional methods. However, these techniques have some limitations, such as the long time for the development and optimization of each assay, especially for multiplex PCR, real-time PCR, etc. (Kellogg et al., 2012; Fischer et al., 2008). Furthermore, many viruses are refractory to culture, and analysis by electron microscopy can be difficult depending on the type and morphological characteristics of the virus. Therefore, microarray techniques are increasingly used, with reduced analysis time and the possibility of detecting hundreds of thousands of genes in a single experiment (Donatin and Drancourt, 2012; Wang et al., 2002; Fischer et al., 2008; Peterson et al., 2010).

Many pathogenic bacterial strains vary in their ability to cause disease. Thus, techniques for detecting genes encoding virulence factors are of great importance for the identification

and characterization of bacterial pathogens. Screening pathogenic bacterial strains for genetic elements can provide important information about how virulence factors are acquired by pathogenic bacterial strains (Peterson et al., 2010).

An important application of microarray technology is the clinical diagnosis of infectious diseases (Cao et al., 2017). With the help of the microarray technique, rapid and accurate detection of bacteria and viruses from various samples: blood, urine, cerebrospinal fluid and respiratory secretions can be achieved. The technique can be used to diagnose various infections of the respiratory, gastrointestinal and central nervous system. In the case of acute respiratory infections, the simultaneous presence of several respiratory viruses can be detected: influenza virus, respiratory syncytial virus (RSV) and coronaviruses, including SARS-CoV-2. Thus, the microarray technique can be used for rapid and accurate diagnosis. The technique is also used for the detection of antimicrobial resistance, for the detection of *Neisseria meningitidis*, for the identification of mutations, but also for the adaptation of vaccination and treatment strategies (Damin et al., 2021; Wang et al., 2020; Asmare and Erkihun, 2023).

Microarray technology is also used in pathogenicity studies to better understand the molecular mechanisms by which bacteria and viruses cause disease. The pathogenesis of infections, as well as the genes and signaling pathways involved in virulence, can be determined by comparing the gene expression profiles of different pathogens. Thus, microarray technology can be used to identify virulence genes in pathogenic bacteria, such as *Staphylococcus aureus*. Such studies have led to the discovery of new strategies for the development of antibiotics and vaccines, leading to improved mechanisms to combat bacterial infections (Moneche and Ehricht, 2005; Zhu et al., 2007).

Detection of genes involved in cancer

Cancer is a complex disease characterized by genetic and epigenetic changes that lead to uncontrolled cell division, playing an important role in its early diagnosis. The gene expression of a cell determines how it manifests itself, its function, but also its response to different stimuli. With the help of gene expression profiles, regulatory mechanisms, but also cellular functions can be determined. For the early detection of cancer, the commonly used methods (classical imaging methods and morphological analysis of tissues or cells) have certain limitations. The microarray technique is a modern technique that allows the understanding of the molecular mechanisms of cancer, early diagnosis, prognosis and the development of targeted therapies. Microarray technology has thus become an essential technique in cancer research, allowing the analysis of gene expression and the identification of genetic variations (Schena, 2000; Wikman et al., 2000).

Oligonucleotide microarrays have been used as a method for rapid analysis of mutations in selected gene sequences and are effective in sequence analysis, genetic disease diagnosis, and gene polymorphism studies. cDNA microarrays are commonly used for gene expression analysis, and their use is relatively easy (Wikman et al., 2000; Yershov et al., 1996). Researchers hypothesized that the genes expressed by the two tumor types (BRCA1 mutation carriers vs. BRCA2 mutation carriers) are distinct. An analysis of the variation between gene expression levels and sample genotypes identified 176 genes that were differentially expressed in BRCA1-mutated tumors and BRCA2-mutated tumors. Yuan et al., (2003) used cDNA microarrays to identify gene expression patterns among

colorectal cancer cell lines and to directly compare lines with and without microsatellite instability. Several differential expression patterns were identified (Hedenfalk et al., 2001; Yuan et al., 2003). Characterization of DNA copy number is important for both the basic understanding of cancer and its diagnosis. cDNA microarrays have been widely used to characterize human gene expression variation (Gupta et al, 1999; Pollack et al., 1999).

Microarray-based expression profiling allows the identification of gene families as well as important molecular and cellular events that may be essential in complex processes such as metastasis. In the future, practical applications relate to the diagnostic and prognostic organization of patients. To determine the mechanisms of action of drugs, as well as their sensitivity and toxicity, the microarray technique can be used in clinical trials. Thus, microarrays are useful for developing studies of molecular taxonomy of cancer, including the organization of cancer types into groups, based on gene expression profiles. Therefore, the microarray technique can be used for: molecular phenotyping, the study of gene function, functional genomics and pharmacogenomics (Pollack et al., 1999).

Studies have illustrated the efficacy of microarrays in oral cancer, through gene expression analysis. Early diagnosis and management of oral cancer is correlated with increased survival (Alevizos et al., 2001).

Because cancers result from the accumulation of many genetic and epigenetic alterations, microarray technologies are important in cancer research although there are some disadvantages to the routine use of microarrays. The cost of microarray experiments can be quite high due to the need to standardize the technique and to develop data analysis methods that allow comparison of data between different research groups. However, microarray techniques are considered important methods in cancer research. Using oligonucleotide microarrays, early diagnosis of cancer can be achieved, and gene expression profiling can be used to obtain prognosis after chemotherapy or radiotherapy (Kim et al., 2004).

Genetic polymorphism detection

Genetic polymorphisms refer to DNA sequence variations that occur within a population and that can determine different phenotypic traits, susceptibility to disease, and response to different treatments. The identification and characterization of genetic polymorphisms are important for understanding personalized medicine and genetic association studies. Microarray technology has revolutionized the detection of polymorphisms, providing a rapid, accurate, and high-throughput method for analyzing genetic variation (LaFramboise, 2009).

In clinical diagnosis, polymorphism-based microarray analysis allows the detection of copy number variations (CNVs). A single nucleotide polymorphism (SNP) is a variation at a single position in a DNA sequence between individuals. It is a common genetic variation in which a single nucleotide (A, C, G, or T) is replaced by another nucleotide at a specific locus in the DNA sequence. Each SNP locus in the genome can have up to four versions, one for each nucleotide (Arsham et al., 2017; Auton et al., 2013; Palmisano et al., 2005).

To date, there are over 200,000 single nucleotide polymorphisms (SNPs) associated with traits or diseases, according to the Genome-Wide Association Studies (GWAS) catalog, which is a database of genome-wide association studies. However, not all SNPs associated with diseases are directly responsible for the development of a disease. Some SNPs are linked to other genetic variants that are directly involved in the occurrence of

the disease. In addition, the effect of SNPs on disease risk varies depending on different factors, such as: environment, lifestyle and interactions with other genes (Uffelmann et al., 2021).

The microarray technique also has some limitations, as it cannot ensure the detection of unknown SNP mutations. Moreover, the use of large data sets requires the use of complex analysis and calculation methods, the cost of chip preparation, reagents and equipment being quite high (Ahmad and Iqbal, 2012; Iwamoto et al., 2007; Hirchhorn and Daly, 2005).

A frequently used application of gene expression analysis is the scanning of the entire genome to identify SNPs associated with phenotypic traits and various diseases. SNP microarrays are important in these analyses, and allow the simultaneous analysis of millions of genetic variations in large population samples. These studies have led to the discovery of new genes and molecular pathways involved in complex diseases, such as diabetes, cardiovascular disease, and cancer (Hirchhorn and Daly, 2005; Shastry, 2006).

Identification of genetic polymorphisms by microarray is important for the development of personalized medicine. Genetic analysis of SNPs can provide important information about individuals' susceptibility to certain diseases, drug response, and risk of developing adverse reactions to certain drugs. For example, microarray tests can identify variants in the CYP2C19 gene to guide treatment with anticoagulant drugs such as clopidogrel. The importance of these genetic identifications for developing personalized treatments, improving therapeutic efficacy, and reducing adverse reactions is also emphasized (Shastry, 2006).

Microarray techniques are also used in the diagnosis of genetic diseases by detecting pathogenic mutations and chromosomal variations. CGH microarrays can identify CNVs associated with genetic syndromes, such as DiGeorge syndrome and Williams-Beuren syndrome. These techniques can accurately identify chromosomal deletions in the 22q11.2 region, the characteristic region of DiGeorge syndrome, which contains several genes important for normal development, the loss of which can lead to the symptoms associated with the syndrome. Microarray techniques are being developed to allow precise detection of the exact size and location of the deletion. SNP microarrays can also detect mutations associated with monogenic diseases such as cystic fibrosis and hemophilia (Shastry, 2006; McDonald-McGinn and Sullivan, 2011).

Conclusions

Microarray technology is revolutionizing the way biological research is conducted, as it allows the simultaneous analysis of thousands of uniquely identified genes in a single experiment. Various variants of microarrays have been successfully used, alone or in combination, in biological research, medical diagnostics, drug discovery and development, and toxicogenomics, leading to an acceleration of progress in current fields.

Although microarray techniques can be improved technologically, the results and conclusions of published studies have clearly demonstrated the utility and power of these miniaturized tools. Microarray-based clinical diagnostic tools can represent a basis for personalized medicine.

Although microarrays are primarily research techniques, microarray-based approaches are rapid and flexible.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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