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Review Article

Review on DNA Micro Array Technologyand Its Application

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Abstract: DNA microarrays are technology that measure the expression level of thousands of genes at the same time. They need become avital tool for a good kind of biological experiments. one among the most common goals of polymer microarray experiments is to spot genes related to biological processes of interest. DNA Microarray is one such technology that allows the researchers to analyze and address problems that were once thought to be non traceable. This technology has scepter the scientific community to manage the elemental aspects underlining the expansion and development of life, additionally on explore the genetic causes of anomalies occurring within the functioning of organisms. Microarrays area unit vital as a result of they possess a large variety of genes and additionally owingto their transportable size. An important implication of the fundamental dogma of molecular biology is that there should be a strong association between the presence of a given protein in a cell and the presence of the mRNA sequence that is transcribed to build that protein. If a protein is active in a given cell, there should be a large number of copies of the mRNA sequence corresponding to that protein. Conversely, if a protein is not active in a cell, there should be few copies of the corresponding mRNA sequence. Thus, DNA microarrays attempt to evaluate the presence or absence of proteins in a cell and their relative abundance by measuring the relative abundance of the corresponding mRNA sequences. This review addresses the potential uses of DNA microarray technology, principle of the technology, its application and limitation of the technology.

Keywords: DNA Microarray, Protein Microarray, Hybridization, cDNA

1. Introduction

Molecular analysis method are continue to increase in utility in clinical microbiology laboratories. The implementation of in vitro nucleic acid amplification techniques, led by real time PCR, in diagnostic laboratories has trans formed viral detection and select bacterial detection. The further advancement of molecular infectious disease diagnostics is dependent on the capacity of multiplexing technologies, or the ability to detect and isolate more than one pathogen simultaneously from the same specimen, to be implemented in clinical microbiology laboratories with easy and accuracy. One approach to multiplex detection and characterization is microarray analysis. Simply defined, a microarray is a collection of microscopic features (most commonly DNA) which can be probed with target molecules to produce either quantitative (gene expression) or qualitative (diagnostic) data. Although other types of microarrays exist, such as protein microarrays [19, 20] this review will focus on DNA microarray sequencing. Microarray detection is usually combined with PCR to detect specific amplicons. The inclusion of many different "probe" sequences on one microarray allows simultaneous detection of different organisms, or differences between organisms of the same species [35].

DNA microarrays have become a widely used standard tool in molecular biology during the last decade and they can be used for a number of purposes including gene expression profiling and alternative splicing analysis, comparative genomic hybridization analysis (CGH) to discover genetic amplifications and deletions, chromatin immunopercipitation on chip (ChIP) to detect binding sites of DNA binding proteins or genotyping by single nucleotide polymorphism (SNP) detection and fusion gene analysis [40].

DNA microarray technology can be used for measuring the relative abundance of the biological sequences of interest in a

given sample. The technology is based on a use of fluorescent labeled and slide attached interrogation probe sequences. The technology takes advantage of the ability of the complementary single-stranded sequences of nucleic acids to form double stranded hybrids [30].

Microarrays are the method of choice for studying diversity of microbial communities, and will continue to be used despite the advent of accessible next-generation sequencing techniques. Relative quantification of differences between samples is possible using this technique. DNA sequences acting as probes are fixed on tiny slides in arrays to identify the presence of tagged fluorescently nucleic acids from a certain sample. The nucleic acids having complementary sequences with probes will hybridize on the array slides and because they are labeled, they are detected easily using specialized scanner and software [27].

Objective: To review DNA microarray technology, principle, its application and limitation of the technology.

2. Microarray Technology

Microarray is a technology which allows quantitative, simultaneous monitoring and expression of thousands of genes [1]. It is made up of glass slides or chips coated with up to hundreds of chemically synthesized short sequences oligonucleotide probes. Though microarrays were initially used for the study of gene expression, but recently, oligonucleotideDNA microarray has been widely used in the field of food borne pathogen detection had reported the detection of pathogenic Shigella and Escherichia coli serotypes by this method for the first time. In general, this method is highly sensitive and allows simultaneous identification of multiple food borne bacterial pathogens. However, this system requires specialized instruments and trained personnel in order to run the experiments. Characteristically microarray consists of oligonucleotides which are several large nucleotides long attached to the surface of a glass slide. Using appropriate photolithographic masks, a single nucleotide A, C, T, or G is attached at a time, and therefore it is possible to construct a microarray with hundreds of thousands of different oligonucleotide sequences which are complementary to characteristic fragments of known DNA or RNA sequences. These characteristic fragments are arranged in sets called probes [23]. Since most biological phenomena are within the context of a multitude of parameters and processes, the correlations and interactions of these processes are at the centre of quantitative biological investigations. The interrogation of a broad variety of genes or their transcripts and their activity at one moment is one of the typical questions; and parallel analysis is needed since it can be performed by the use of microarrays.

DNA microarrays are characterized by a structured immobilization of DNA targets on planar solid supports allowing the profiling of thousands of genes or interactions in one single experiment. An ordered array of these elements on planar substrates is called a “microarray”. Usually, for practical reasons, one the difference being between microarrays and macroarrays, distinguished by size of the dispensed spots. Typical spot sizes of macroarrays are featured by a diameter of more than 300 microns, whereas microarray spots are represented in less than 200 microns.

The basic principle behind microarray is the base complementarities, i.e., the base pair ‘A’ is complementary to ‘T’ and ‘C’ is complementary to ‘G’. In a microarray, many thousands of spots are placed on a rectangular grid with each spot containing a large number of pieces of DNA from a particular gene. When the sample of interest contains many copies of mRNA, many bindings will occur, indicating that the gene from the transcribed mRNA is highly expressed. The quantity of hybridization can be determined because each copy of mRNA is labeled in the experiment with a fluorescent or radioactive tag and a brighter signal is detected when more copies bind [18]. In general, all microarray assays contain five discrete experimental steps – biological query, sample preparation, biochemical reaction, detection, data visualization and modeling [32]. Atypical microarray experiment involves sample extraction, fluorescent labeling, co hybridization, scanning and finally statistical analysis. Microarray technologies can be broadly categorized into DNA microarrays and protein microarrays.

2.1. DNA Microarrays

DNA microarrays are widely used to measure gene expression levels following the outlined procedure. A DNA or ribonucleic acid (RNA) sample, representing the pool of expressed genes isolated from biological sources, is first amplified and labeled with a fluorescent dye. The power and universality of DNA microarrays as experimental tools derives from the exquisite specificity and affinity of complementary base-pairing [3]. DNA Microarray technology has empowered the scientific community to understand the fundamental aspects underlining the growth and development of life as well as to explore the genetic causes of anomalies occurring in the functioning of the human body [4].

DNA microarrays are oligonucleotide arrays and a variety of cDNA arrays.

2.1.1. Oligonucleotide Arrays

Oligonucleotide arrays or DNA chips are miniature parallel analytical devices containing libraries of oligonucleotides robotically spotted (printed) or synthesized in situ on solid supports (glass, coated glass, silicon or plastic) in a such way that the identity of each oligonucleotide is defined by its location [37] Oligonucleotide arrays contain short fragments of DNA (25 base pairs). One of the commercially available oligonucleotide microarrays are the Gene Chips developed by firms such as Affymetrix. Ten to hundred thousands of different oligonucleotide probes are synthesized on each array. Traditionally, Affymetrix Gene Chip Arrays are manufactured as a single array caged in a sealed cartridge with glass as a substrate. The oligonucleotide technology pioneered by Affymetrix Gene Chips differs from cDNA microarray in two important respects [9]. First, the probes are a set of 20-25 short oligonucleotides that are specific for each gene or exon, along

with the related set with single base mismatches incorporated at the middle position of each oligonucleotide. These are synthesized in situ on each silicon chip using genome sequence information to guide photolithographic deposition. Second, the arrays are hybridized to a single biotinylated amplified RNA sample, and the intensity measure for each gene is computed by an algorithm that messages the difference between the match and mismatch measurements, and averages over each oligonucleotide. Key difference between gene chips and a cDNA microarray is the way genes are represented on the arrays. In in situ photolithographic synthesis method used by Affymetrix gene chip probe arrays, the quality of chips produced depends critically on the efficiency of photo-deprotection [2].

2.1.2. cDNA Arrays

cDNA arrays contain long fragments of DNA (from 100 to thousands of base pairs). cDNA arrays are created by robotically spotting individual samples of purified cDNA clones onto a solid support (glass slide or membrane). Some of the basic principles behind preparation of cDNA arrays includes: i) selection of the targets to be printed on the array directly from databases such as GenBank, dbESt, and UniGene or randomly from any library of interest; ii) arraying the selected cDNA targets onto the known location of coated glass microscope slide using a computer-controlled high speed robot; iii) fluorescently labeling the total RNA from both test and reference samples using dyes with a single round of reverse transcription; iv) pooling the florescent target for hybridization under stringent conditions; v) measuring the laser excited incorporated targets using a scanning con focal laser microscope; and v) finally, analyzing the images from scanner by importing into a software in which they are pseudo-colored and merged. Micro spotting, piezoelectric printing and photolithography (an 'in situ' fabrication technique developed by Affymetrix) are some of the techniques used for arraying cDNA [11].

2.2. Protein Microarray

Though DNA microarray is very useful, it has several limitations. The expression levels of many genes are subject to significant posttranscriptional regulation and many proteins are grossly affected by post-translational modification such as phosphorylation, glycosylation, acetylation, proteolysis etc. Obviously, a nucleic acid-based array is blind to such effects and for certain applications, the tedious sample preparation requirements of DNA microarrays make them impractical [18]. The solution for this is to analyze proteins rather than make inferences based on RNA levels directly which can be done through protein microarrays. Protein microarrays also known as protein chips are nothing but grids that contain small amounts of purified proteins in high density. The proteins can be screened in a high through put fashion for biochemical activity, protein–protein, protein–DNA, protein–RNA and protein–ligand interactions. Protein microarrays can be major categorized into three types [12] analytical microarrays, functional microarrays, and reverse phase microarrays. Analytical microarrays are the ones in which bio molecular recognition molecules are immobilized on a heterogeneous matrix using micro printing or micro structuring process. Hapten and antibody microarrays are some of the most common analytical microarrays. Among the several subgroups of protein biochips such as peptide arrays, antibody arrays, cell based arrays, etc, antibody arrays are the widely used ones.

3. Principle of DNA Microarray

The basic principle underlying microarray technology is that complementary nucleic acids will hybridize. This is also the basis for traditional gene expression analyses, such as Southern and Northern blotting. Hybridization provides exquisite selectivity of complementary stranded nucleic acids, with high sensitivity and specificity. In the traditional techniques, in which radioactive labeling materials are usually used, the simultaneous hybridization of test and reference samples is impossible. In microarray-based technologies, the solid surface, such as a glass slide, contains hundreds to thousands of immobilized DNA (targets) spots which can be simultaneously hybridized with two samples (probes) labeled with different fluorescent dyes [6, 13].

As mentioned earlier, the whole technique is based on matching unknown and known DNA samples via Watson-Crick base pairing principle [27]. The known DNA samples are known as 'probes' and are spotted and fixed on microscope glasses or silicon chips in thousands. These can be oligonucleotides, cDNA, or even just DNA [22]. On the other hand, the unknown DNA samples are the ones we want analyze their gene expression level for example and are tagged using reporter molecules like fluorophores which replaced radioactive molecules due to their potential health risks. Main steps in measuring gene expression levels in a biological sample using DNA microarray technology includes: sample preparation and tagging, hybridization, washing, image acquisition and normalization [25].

3.1. Sample Preparation and Tagging

First, mRNA has to be extracted from the biological sample of interest and purified. A control must be included in the experiment as well (e.g. diseased tissue vs. healthy tissue). Next, the tagging involves performing reverse transcription reaction to synthesize complementary DNA (cDNA) strand [36]. In this method, poly T primer is attached to mRNA to start the reverse transcription process from the polyadenylation signal at the 3' un-translated site (UTR) of the mRNA. A proportion of the nucleic acids: dATP, dGTP, dCTP, and dTTP added in this reaction are incorporated with a florescent dye (e.g. only dCTP labeled with Cy) via covalent bonding [16]. Diseased and healthy samples can be also tagged with different dyes such as Cy3 (Excited by a green laser) and Cy5 (Excited by a red laser) to distinguish between them and are used in the same microarray. Thus, cDNA probes complementary to the tagged transcripts will hybridize and eventually visualized as colored spots under the camera.

3.2. Hybridization

In this step, the DNA probe on the micro-slide glass and the tagged target cDNA will pair according to Watson-Crick configuration [14]. This can be accomplished either manually or using robotics system. In the first approach, the array is placed in a special chamber where the researcher injects the solution containing the target cDNA onto the array under sterile conditions and incubates it at certain temperature for 12 to 24 hours [26]. According to the second approach, everything is performed by a programmed robot which saves time and effort, performs the protocol at specialized station, and grants a better control over the temperature that is usually between 45 and 65°C. It is also important to mention that hybridization is affected by many conditions such as salt concentration, temperature, form amide concentration, humidity, and amount of target solution. For example, higher temperature and lower salt concentration will increase stringency meaning that only specific strands will hybridize. In order to limit or prevent cross-hybridization, a repetitive DNA sequence and poly T or poly A can be added to mask the genomic repeat sequence and the polyadenylation sites on the cDNA respectively [33].

3.3. Washing

Eliminating excess hybridization solution from the microarray is one of the reason why this step is crucial as it makes sure that only tagged target cDNA that we want to measure is bound on the microarray [17]. In addition, washing raises the stringency by limiting cross-hybridization. Researchers can use low salt concentration solutions that contain 0.1× SDS, and 0.1× standard saline citrate (SSC). Many automated hybridization stations may include a washing cycle as part of the whole process [5].

3.4. Image Acquisition

This can be considered as final step in the experimental process where an image of the results is taken. Because the target bound cDNA is tagged with florescent dyes, these can be excited by a light of a suitable wavelength giving certain colors [30]. Thus, micro slides are placed under scanner having two lasers (For example to excite two different dyes for diseased and healthy tissues) to be read. For better accuracy, the optics are shifted on the whole slide to read every point on the microarray as well as setting pixel size (Represents size of the physical space) to be same as the laser spot to ensure that light read is not coming from neighboring spots on the microarray [39].

3.5. Normalization

Keeping in mind that there might have been some errors arising from image acquisition, one could carry a process to correct for bias within microarrays before final analysis [31]. This is known as normalization and it serves as ‘calibration’ to remove systematic variations between samples. Some of the several inconsistencies could include different scanner settings, hybridization properties, and dye efficiencies. These have a great effect on experimental results and therefore may result in misleading conclusions about DNA analysis. Although there are various normalization methods, LOWESS is commonly used and it detects systematic variations by linear regression as function of the log10 (In case of intensity) and balance the observed ratio with best fit average long2 (In case of ratio). After normalization, expression ratio, which is the normalized value of expressed gene over that of the control, can be calculated using the following formula: Ti = Ri / Gi, where i represents the gene, and R (Red) and G (Green) representing target and control respectively. If we use Ti =log2 (Ri / Gi) instead, this will expands the dynamic range of gene expression level signals [38].

4. Application of DNA Microarry

The DNA microarrays technology is wide wont to live levels of organic phenomenon. Alternative applications will embrace genotyping wherever scientists will find single ester polymorphisms (SNPs), that are variety of genetic variation among individuals because of a distinction in single nucleotide [29].

4.1. Disease Diagnosis (Sickness Identification)

Microarray technology can facilitate researchers to find out a lot of regarding many various diseases, as well as heart condition, mental state and infectious diseases, to call solely a couple of. within the past, scientists have classified differing kinds of cancers supported the organs during which the tumors develop. With the assistance of microarray technology, however, they'll be able to more classify these kinds of cancers supported the patterns of sequence activity within the growth cells. Researchers can then be able to style treatment ways targeted on to every specific variety of cancer [4].

4.2. Drug Discovery

Medical chemistry has more and more utilized microarrays to spot each key target sequences and gene networks which will regulate the effectiveness of medicine. One vital application of deoxyribonucleic acid microarray technology, among the context of medicine effectiveness and safety analysis studies, is its use as a screening tool for the identification of organic chemistry pathways, potential targets for novel molecular medicine, for the identification of molecular mechanisms of toxicity and to know and predict individual drug sensitivity and resistance [4].

4.3. Pharmacological Medicine Analysis

One vital application of microarray technology, among the context of neurotoxicological studies, is its use as a screening tool for the identification of molecular mechanisms of toxicity. Such approaches change researchers to spot those genes and their product (either single or whole pathways) that are concerned in conferring resistance or sensitivity to poisonous substances [4].

4.4. Array Primer Extension

In genotyping single ester polymorphisms is mistreatment Array Primer Extension Assay, additionally called APEX [28] this can be a lot of useful than alternative laboratory assay because it contributes to lower chemical agent prices because of little reaction volumes, e.g. little slides. the most principle of APEX is that oligonucleotides are placed on the microarray glass slide through their 5' end and complementary PCR amplified fragment from deoxyribonucleic acid sample is treated to the oligonucleotides [24] after ward, deoxyribonucleic acid enzyme extends the 3' ends of primers with dye labeled nucleotides (e.g. ddNTPs) via sequence specific single ester extension [29].

4.5. Immunological Study

DNA microarray technology has been applied in medical specialty researches like the event, maturation, activation and differentiation of immune cells, the regulation of immune responses, the molecular mechanism of allergic reaction, the relation between makeup and organic phenomenon, and medical specialty pharmacological medicine, etc. it's concentrated our perception of the system.

It will further be useful within the analysis of the regulatory mechanism of ancient Chinese medication (TCM) to ward immune cells and immune responses, the therapeutic mechanisms of TCM toward allergic reaction, the standardization of differentiation of syndrome and flavoring pharmacological medicine, etc [4, 21].

4.6. Determination of Antimicrobial Drug Resistance

Another winning application of microarray techniques in clinical biological science is that the determination of antimicrobial resistance by at the same time police work a panel of drug resistance connected mutations in microbic genomes [7, 41]. Oligonucleotide microarrays were developed to research and establish drug-resistant Mycobacterium tuberculosis infectious disease strains, and it had been found that the results were comparable those of ordinary antimicrobial susceptibleness testing [10]. One of the many application areas of the microarray format is to genotype or detect disease‐causing or disease‐predisposing mutations in the human genome for diagnostics, carrier identification and pharmacogenetic profiling. To observe DNA mutations To study genomic gains and losses.

5. Limitation of DNA Micro Array

The technology is too expensive and the arrays provide an indirect measure of relative concentration Especially for complex mammalian genomes, it is often difficult to design arrays in which multiple related DNA/RNA sequences do not bind to the same probe on the array [8]. A DNA array can only detect sequences that the array was designed to detect That is, if the solution being hybridized to the array contains RNA or DNA species for which there is no complimentary sequence on the array, those species will not be detected. For gene expression analysis, this typically means that genes that have not yet been annotated in a genome will not be represented on the array. In addition, non-coding RNA's that are not yet recognized as expressed are typically not represented on an array. Moreover, for highly variable genomes such as those from bacteria, arrays are typically designed using information from the genome of a reference strain. Such arrays may be missing a large fraction of the genes present in a given isolate of the same species. For example, in the bacterial species Aggregate the gene content differs by as much as 20% between any two isolates [15]. Hence an array designed using gene annotation from a "reference isolate" will not contain many of the genes found in other isolates.

6. Discussion

DNA microarray technology is advancement of molecular communicable disease nosology relies on the capacity of multiplexing technologies, or the power to observe and isolate quite one infective agent at the same time from constant specimen, to be enforced in clinical biology laboratories with ease and accuracy. Microarray could be an assortment of microscopic options (most usually DNA) which may be probed with target molecules to provide either quantitative (gene expression) or qualitative (diagnostic) knowledge. DNA microarrays became a wide use common place tool in biology throughout the last decade and that they is use for variety of functions as well as organic phenomenon identification and various junction analysis comparative genomic crossbreeding analysis to get genetic amplifications and deletions, body substance immune precipitation on chip to observe binding sites of DNA binding proteins or genotyping by single ester polymorphism (SNP) detection and fusion factor analysis [40]. Microarray technologies can be broadly categorized into DNA microarrays and protein microarrays. InDNA microarrays the oligonucleotide arrays and a variety of cDNA arrays incorporated [4]. Protein microarrays can be major categorized into three types [12]: analytical microarrays, functional microarrays, and reverse phase microarrays. The core principle behind microarray is hybridization, also there are five major steps are performed in typical microarray experiments. Those steps are: sample preparation, hybridization washing, image acquisition and neutralizations and data analysis. DNA microarray technology are applied in various biological purpose instead of diagnosis, drug discovery immunology, antimicrobial drug resistance, Array Primer Extension and for toxicological research [4, 29]. DNA microarray have some limitation such as: The results take a lot of time to analyze as the amount of data collected from each array will be huge. The results may be too complex to interpret and are not always quantitative. The technology is too expensive and the arrays provide an indirect measure of relative concentration Especially for complex mammalian genomes, it is often difficult to design arrays in which multiple related DNA/RNA sequences do not bind to the same probe on the array. A DNA array can only detect sequences that the array was designed to detect.

7. Conclusions

Microarrays area unit the tactic of selection for learning diversity of microbic communities, and can still be used despite the arrival of accessible next-generation sequencing techniques. Relative quantification of variations between samples is feasible victimization this method. For nosology, microarrays still provide variety of benefits over different techniques for reason that the high capability for multiplexing. The step that's limiting the commercialization and additional development of microarrays for organism identification is that the complexness and also the time needed to style and take a look at discriminatory genetic regions that separate one species from another. This same lack of discriminatory information moreover limits different molecular identification ways, as well as sequencing.

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