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Microarray tools for deciphering complex diseases

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1. ABSTRACT

Individual genetic findings associated with complex diseases are unlikely to fully explain their substantial impact or provide new comprehensive insights into disease pathogenesis. These also lack the comprehensive data much needed for development of new effective drugs in majority of the disease cases in a population. In fact multilevel etiologic factors underlie almost all human diseases, including: environmental causes, epigenetic factors, DNA mutations, amplifications, and deletions, RNA expression levels, protein (translation, post translation modification, localization) and combinations thereof. Each individual might consist of different combinations of these multiple etiologic factors. Integrative evaluation of all these modifications will shed light on the whole identity of the disease and the underlying molecular mechanisms. Until now it was inconceivable to have a full grasp of such a complex etiology. Microarrays enable us to interrogate the individualized various factors (DNA, RNA and protein content) involved in disease state on genome-wide scale simultaneously and expeditiously in single cell or the tissue of interest (Figure 1).

The new disciplines of microarray studies in combination hold the promise of effective, current, and comprehensive understanding of complex diseases and may be a good approach for reducing the costs and time lines associated with discovery and efficacy improvement of therapeutic drugs. In the future, through utilizing the colossal amount of microarray data findings, defining the structure, function, and dynamics of entire biological pathways and cellular networks under various physiological states, and the development of robust and efficient methods for analyzing and interpreting high dimensional data, it will be possible to connect combination of experimental results with individualized disease state. This will facilitate precise diagnosis prognosis and therapy.

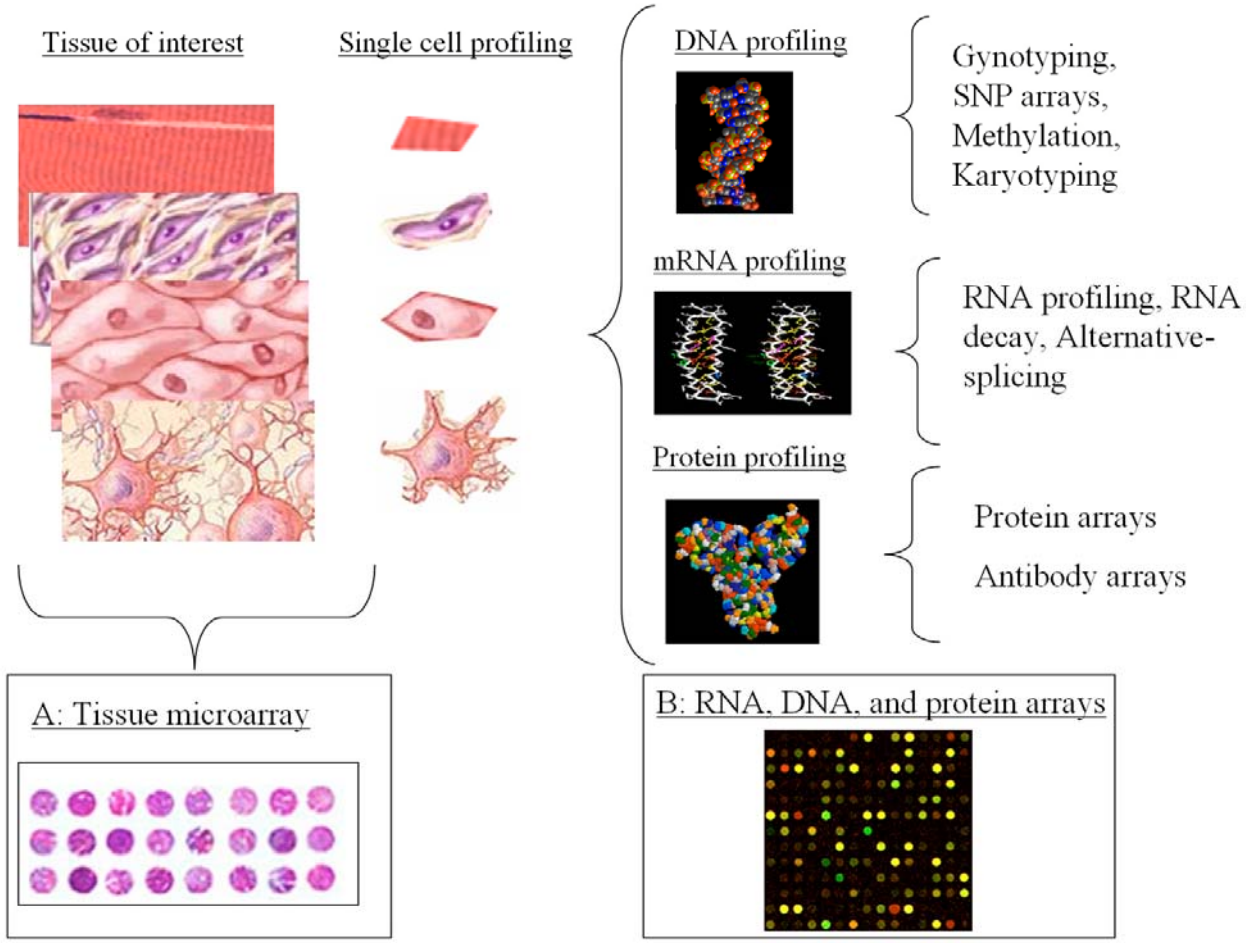

Figure 1. Levels of disease exploration by microarrays: Tissue of interest or single cell can be profiled for their DNA, RNA and protein content by genotyping, SNP, methylation, karyotyping, expression, alternative splicing and protein profiling (A). The tissue itself may be explored by tissue microarrays. Lower panel shows examples of images in result of tissue microarray experiment (B) or DNA, RNA, and Protein microarrays (C).

2. INTRODUCTION

Recent complementary advances in genomics knowledge and technology miniaturization are beginning to overcome the intricacies of exploring complex diseases (1,2). These discoveries are especially accelerated by microarrays, which we review here. Microarrays are small, solid supports onto which thousands of different elements (oligonucleotides, proteins, cells, cell extracts, and tissues) are immobilized, at fixed locations (3-6). The support surfaces are usually glass microscope slides (7). The power of microarray analysis lies in its miniature platform features, which facilitates relatively rapid global exploration of the systems studied.

Microarrays have been implemented in a variety of manners (8). Gene expression profiling, one of the first applications of microarrays, has shown its great potential (2). It is an especially powerful analytical tool for complex diseases because of the multi etiology characterized by a combination of genes involved in development of complex diseases (9-12). By profiling the global RNA content of any cell, it is possible to monitor in parallel all expressed genes to explore any abnormalities in diseases (13,14). Using this technique, researchers have been uncovering rapidly new genes and pathways involved in complex diseases and discovering novel treatment targets (15-17). Moreover, the microarray technique has been shown to be useful for patient management as a precise molecular device for diagnosis, prognosis and, personalized treatment (18-20). More recently, new emerging applications of the microarray technology are revealing other aspects of vital balance in the complex dynamic behavior of cells including genomic content (21), epigenetics (22) and protein status and profile (23).

Achieving successful discoveries of the etiology and new drug development schemes for complex diseases will require a merger of all microarray experimental applications and research disciplines that include pharmacology, genomics, comparative genomics, functional genomics, proteomics and bioinformatics (Figure2). DNA, RNA and protein profiling by microarrays can be assessed in existing states or following introduction of external effects.

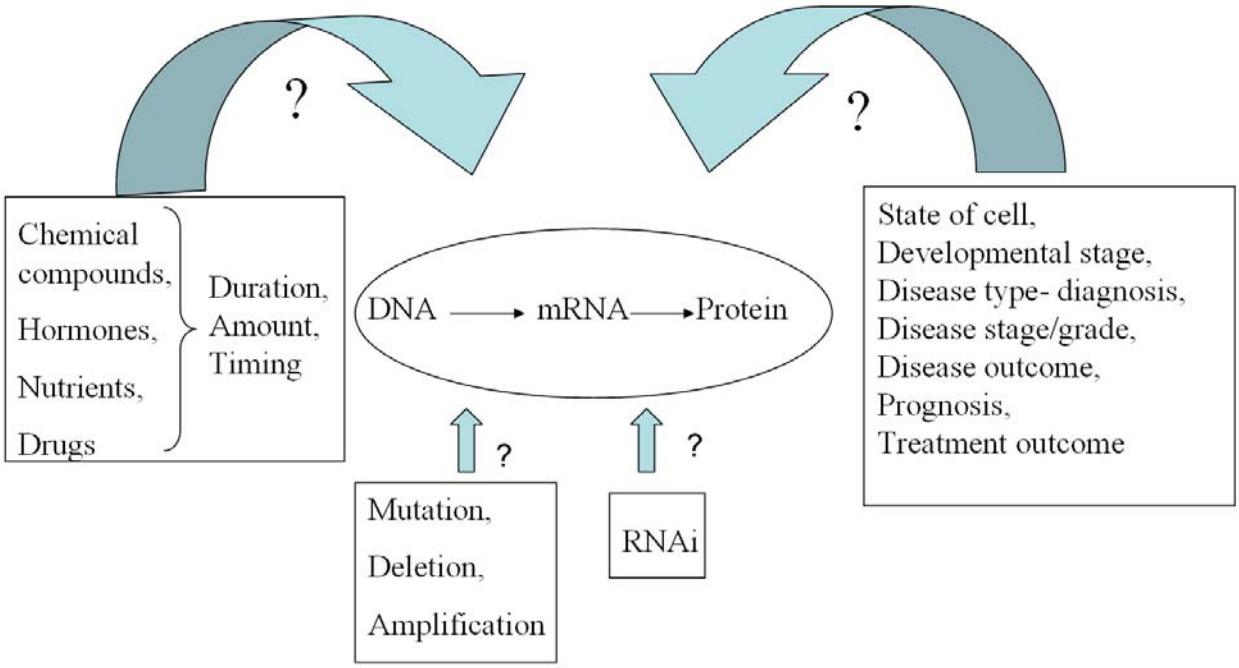

Figure 2. Experimental uses of microarrays: Microarrays can be used to assess DNA, RNA and protein profile in existing states or explore changes following introduction of effects as chemical compounds, hormones, nutrients, and drugs in certain intervals, doses and timing. Microarray experiments following RNAi will assess the effect of elimination of any RNA and microarray experiments after DNA mutations, deletions and amplification will assess the effect of DNA content on the state of the cell.

3. GENE EXPRESSION (RNA) PROFILING

The fate of any cell is determined largely by the subset of genes it expresses. This governs the cell's behavioral characteristics, the type of tissue it constructs and whether it is normal or diseased. Activation or expression of a specific combination of genes, in precise amounts and in a timely manner, is crucial for a cell's normal activity. The pattern of the transcriptional deregulation provides insight into the cause of abnormal features. This can be facilitated by the study of global gene expression in tissue and cells. The Human Genome Project has resulted in an exponential growth in the amount of information available about the DNA sequence of the human genome (24,25). Consequently, researchers have identified a large number of novel genes within these previously unknown sequences (26). The human genome predicts around 30,000 open reading frames (ORFs) (27). Recent microarray analyses reveal that around 12,000 transcripts are found to be expressed in any given cell type, of which >90% vary even between different "normal" tissues (28,29). The underlying genetic basis of complex diseases is likely to be dictated partly in a combinatorial fashion by the abnormal expression of several to hundreds of genes (30). Thus, analysis of global gene expression patterns has the potential to predict biological behavior, global composition of different cellular states and clinical consequences. Using DNA microarrays, researchers can determine the expression level of hundreds of thousands of genes at the same time, allowing them to compare large sets of genes in different tissues or cells and thereby identifies pathways and regulatory networks (12). Therefore, this technology helps to pinpoint patterns of gene expression associated with disease, assess influences of environmental factors, evaluate effects of therapeutics, and identify molecular markers indicative of disease status and progression risk. These studies will facilitate better understanding of the impact on disease susceptibility onset and progress. The ultimate goal would be to use this knowledge for prevention, early detection and possibly intervention for improvement of patients' well being.

Several microarray expression-profiling approaches can be applied to complex diseases. First, studies designed to identify differences in gene expression in two sample mode (test-control) comparisons. Determination of genes expressed in disease tissue compared with the normal counterpart allows understanding disease pathology and identifying potential points for therapeutic intervention. Other studies can focus on different stages of diseases, different time points of treatments, different individual cells and the different locations. Such studies were implemented in diseases with underling polygenic conditions such as cardiovascular diseases (31) and renal diseases (14). The identification of the genetic variants that confer susceptibility to common autoimmune diseases, such as type 1 diabetes (T1D) and systemic lupus erythematosus (SLE), will provide significant insight into their pathogenesis as well as identifying potential new targets for more-directed therapeutic intervention (32). Recent work on alopecia areata, multiple sclerosis, systemic lupus erythematosus, and Sjeogren's syndrome illustrates the potential for gaining new insights into the pathophysiology of these

complex autoimmune disorders on a global, molecular scale (33,34).

The impact of drug administration on gene expression profiling may reveal the drug target, drug metabolism, and disease pathways. By monitoring these changes in different populations and genotypicaly different patients it is feasible to enhance the drug effect by dosage adjustment and more notably to prevent adverse reactions. Pharmacogenetic studies have indicated the possibility for a more individually based pharmacotherapy for schizophrenia (18) and depression (35). These lines of investigation lead also to mechanisms of toxicity of drugs or toxins for example mechanisms underlying the pathophysiological effect of nicotine and smoking, particularly on endothelial function and pathogenesis of atherosclerosis (36).

3.1. Implementing expression profiling Microarrays in Cancer Medicine

Chip-based analyses of tumors hold great promise for clinical cancer management (20). Gene-expression datasets can be applied clinically to predict accurate diagnosis, prognosis, and possibly even therapeutic options. These will aid the selective surgical procedures and administration of adjuvant chemotherapy and radiotherapy to the patient subsets that will benefit from those procedures (37).

Gene expression profiling holds the means of exploring novel genes and pathways involved in disease etiology and progression (38,39). In some cases, specific cellular pathways have been revealed that can be therapeutically targeted. The findings of microarray studies are beginning to enter clinical practice as novel diagnostic tests (40). Molecular signatures and aberrant pathways and expression of genes were established for many cancer types including: lymphoma (41) anaplastic thyroid cancer (ATC) (42), lung cancer (43), pancreatic cancer (44) and gastric cancer (45).

Molecular identification and classification of tumors by microarray expression profiling proves to be far more refined than the conventional histopathological assessment (26). This is specifically important for atypical clinical presentation or histopathology. By this approach it is possible to determine exact diagnosis of multiclass tumors (46,47). Moreover, molecular expression profiling proves to be extremely helpful in classification of tumor subclasses (48-50) and in the ability to discriminate primary cancer from metastases of extra origin (51).

Personalized prediction of drug response in cancer patients has a great value for optimized therapy. It has long been apparent that patients with cancers of an apparently similar type, for example vary widely in response to treatment with the same drug. Individualization of treatment according to molecular pathology will assess administration of only beneficial therapy. Moreover, a major limitation in chemotherapy is treatment failure due to anticancer drug resistance (52). The emergence of acquired resistance results from host factors and genetic or epigenetic changes in the cancer cells. Gene expression patterns may be correlated with the degree of antiproliferative effect of candidate drug leads (53). Large microarray based studies aim to identify differentially expressed genes associated with acquisition of resistance include: 60 human cancer cell lines used in a drug discovery screen by the National Cancer Institute (54-56), gastric cancer cell lines (57), human hepatoma (58) and diffuse aggressive lymphoma patient specimens (59). Profiling gene expression changes in tumors and surrogate tissues following drug treatment could also in potential identify pharmacodynamic markers for use in confirming the molecular mode of action of drugs during clinical trials (8).

It is now feasible to predict clinical outcome on the basis of gene-expression signatures. This approach has been successful in several studies: diffuse large B-cell lymphoma (59), embryonal tumours of the central nervous system (CNS) (60), clear cell renal cell carcinoma (61) and breast cancer (62). Microarrays can also be used to predict patient's survival time. This prediction is established by comparing expression profiling of tumors from patients with different survival time (long vs. short) to detect survival-related genes and establish novel prognostic markers. Such studies to distinguish between poor and good prognosis were established in lung cancer patients (63), prostate cancer (64), Ewing's sarcoma (ES) bone tumors (65), lymphoid malignancies (66), gliomas (67) and breast cancer (42).

3.2. mRNA decay profiling by microarrays

mRNA decay could also be explored as a factor in the etiology of complex diseases. The level of mRNA expression is regulated by transcriptional and posttranscriptional control mechanisms. Specific *cis*-acting elements within the mRNA and *trans*-acting factors that bind them modulate the posttranscriptional turnover (68). These elements respond to various stimuli such as developmental, nutritional, hormonal, pharmacological, and environmental alterations (69). Using DNA microarrays, global transcript stability profiles can be compared following various cellular impacts to find their impact on the mRNA turnover (70). Using this technique several signaling pathways have been shown to impact mRNA turnover (71).

3.3. MicroRNA Characterization

MicroRNAs (miRNAs) are a recently identified class of post transcriptional gene regulating RNA molecules. These non-coding RNAs play important roles in cell function and development by binding the mRNA sequences of protein-coding transcripts and promoting mRNA cleavage or repression of productive translation (72). By monitoring miRNA expression Sun et al. have identified miRNAs that are selectively expressed in kidney, heart and skeletal muscle (73). Lim et al. transfected tissue-specific miRNAs in to human cells and used microarrays to examine changes in the messenger RNA profile. These miRNAs shifted gene expression to one that resembles the miRNA tissue of origin (74).

3.4. Alternative splicing detection by microarrays

Alternative splicing of premessenger RNA is an important post-transcriptional layer of regulation in eukaryotic gene expression with a qualitative effect on the gene product (75). It can change the transcript to have a new function (76). Splice variation of a large number of genes has been implicated in various cell growth and differentiation processes (75). Several groups have demonstrated microarray-based detection of alternative splicing (77-81). More recently, Fehlbaum et al. used five exon and junction derived probes of 24mer to fully characterize a splice event (82). Recently Le et al. presented a new approach for characterizing changes in alternative splicing revealed from changes in expression. Their detection of alternative splicing is based on detecting systematic anti-correlation between the expression log-ratios of two different samples versus a pool containing both samples (83). Exon body and splice-junction microarrays are a direct method for alternative splicing studies. Using this method Pan et al. analyzed global features of alternative splicing in major mouse tissues and revealed that tissue specific expression profiles is defined by transcription and alternative splicing different sets of gene. Interestingly they revealed that act independently on different sets of genes in order to define tissue-specific expression profiles (84).

4. DNA PROFILING

4.1. Genotyping

Single-nucleotide polymorphisms (SNPs), a position at which two alternative bases occur at appreciable frequency (>1%), are the most frequent type of variation in the human genome (85). SNPs can serve as genetic markers for identifying disease genes by linkage studies in families (86), linkage disequilibrium in isolated populations (87), association analysis of patients and controls (88), and loss-of-heterozygosity studies in tumors (89). Thus, they provide powerful tools for a variety of medical genetic studies (90).

Genotyping microarrays use multiple probe sets to simultaneously interrogate large number of SNPs from an individual. There are a number of microarray genotyping protocols, including Affymetrix GeneChips (91), Tagged/ZipCode Arrays (e.g. SBE-TAGS (92) and arrayed primer extension (APEX) (93). By using four-color microarray-based mini-sequencing assays, it is possible to pool also multiple DNA samples for higher efficiency (94). To prevent population stratification in genetic association studies of complex diseases Tebbutt et al. developed a robust microarray genotyping chip that simultaneously determines the genotypes at 110 null SNP loci in any individual (95). If this chip establishes an association of a disease with null SNPs, this suggests that there is a population subset with different genetic background plus different disease susceptibility. Using DNA microarray-based genotyping and a combination of statistical tools including neural networks Tham et al. yield promising prediction of coronary artery disease risk (96). Yu et al. used oligonucleotide microarray to genotype ethanol metabolizing enzyme genes and successfully established associations with occurrence of alcoholic liver disease (ALD) (97).

4.2. Molecular karyotyping

Array-based comparative genomic hybridization (aCGH) facilitates detection of global gene dosage abnormalities through chromosomal regions gains and losses by total genomic DNA hybridization to an array of mapped sequences. Recent attempts have improved the resolution of array CGH to approximately 1 Mb by establishing a high-density array (98). Ishkanian et al. created the first tiling resolution BAC array with complete coverage of the human genome using 32,433 fingerprint-verified individually amplified BAC clones (99). On the other hand, verified BAC arrays can be constructed for parts of the human genome for focused studies such as telomeric regions (100) individual chromosomes (101,102) or even chromosome regions (103) (104) and regions that are known to have clinical relevance (105). Array CGH have been used to associate aberrations with disease phenotype and for localizing critical genes (101). Several recent studies have shown the potential of array CGH in detecting DNA copy number alterations in breast cancer (106), chronic lymphocytic leukemia (107), bladder cancer (108), pancreatic cancer (109) fallopian tube carcinomas (110), oral squamous carcinoma (111) and gastric cancer (112). New analysis tools have been recently developed to provide analysis platform for array CGH (45).

4.3. Methylation status: epigenetic surveillance

Epigenetic mechanisms have recently been shown to provide an additional level of regulation on DNA behavior (113). Folding and packaging of DNA is linked with several processes including: replication, repair, and transcriptional regulation (114). For example, as a result of changes in methylation status of GC-rich regions, chromatin structure in the promoter can be altered, preventing normal interaction with the transcriptional machinery causing expression repression of hypermethylated islands and activation of hypomethylated islands (115). If this occurs in genes critical to growth inhibition, the resulting silencing of classic tumor suppressor genes could promote tumor progression. It has been shown that abnormally methylation is a widespread phenomenon in cancer (116). The aberrant CpG island methylation can be used as a biomarker of malignant cells and as a predictor of their behavior (117). Recently, considerable advances have been made in hybridization-based microarray technology for genome-wide analysis of methylation (22,118). A DNA chip can be generated, containing hundreds of oligonucleotides designed to discriminate between methylated and unmethylated sequences in gene promoters (119). Thus this technique is a promising tool for mapping methylation changes in multiple CpG island loci and for generating epigenetic profiles in cancer. It will also allow researchers to study the effect of demethylating agents on the methylation status of critical genes, thereby assessing their usefulness in chemotherapy regimens.

4.4. Protein-DNA interaction profiling by ChIP-microarray/ ChIP-chip

Chromatin immunoprecipitation (ChIP) coupled with whole-genome DNA microarrays (ChIP-chip) is a procedure to investigate global interactions between proteins and DNA (120). The chromatin contains gene-specific and chromosomal domain specific histone

modification patterns. These complexes are involved in determination of chromatin accessibility, histone acetylation, methylation, phosphorylation, and ubiquitination, which are crucial for transcription regulation and replication. For example, Reduced Potassium Dependency (Rpd3) is actually a histone deacetylase, which confers gene-specific repression of transcription when recruited by a DNA-binding protein to a particular upstream regulatory sequence (121). Using the ChIP- microarray Kurdistani et al. mapped Rpd3 genomewide binding sites in vivo (122). Jin et al. used this assay to interrogate promoter sequences that bind the estrogen receptor alpha and regulate gene expression (ERalpha) (123).

5. PROTEIN PROFILING

Conventional RNA expression profiling does not assess the status of many of their end products: the proteins. Therefore, differential profiling experiments require combinations of diverse strategies for identifying proteins, quantifying relative expression, assessing covalent and noncovalent interactions, binding to cofactors and interaction partners, protein turnover, as well as post-translational modifications.

Two general types of microarrays are available for protein assays: antibody arrays and protein arrays. Antibody arrays, where antibody mimics are arrayed, measure the presence and concentrations of proteins. On the other hand, functional protein arrays consist of sets of protein or the entire proteome arrayed on one chip. Protein arrays can be used for profiling of biochemical activities and protein-protein interactions.

In spite of the challenge in obtaining specific antibodies, several studies have used a limited number of arrayed antibodies to reveal changes in protein quantity. Sreekumar et al.. spotted 146 distinct antibodies on glass to monitor the alternations of protein quantity in LoVo colon carcinoma cells. Their results revealed radiation-induced up-regulation of many interesting proteins, including p53, DNA fragmentation factor 40 and 45, tumor necrosis factor-related ligand, as well as down-regulated proteins (124). On the other hand Joos et al. used protein arrays to profile antibodies in the serum of patients with autoimmune disease (125). Once proteins are deposited, they can be tested for a variety of biochemical activities including interactions with proteins, small molecules, or nucleic acids, and kinase activities (126,127). Because peptides are much shorter and more stable than proteins, high-density peptide microarrays can be fabricated by direct synthesis of peptides on a surface using photolithography or light-directed synthesis (128). Protein microarrays are proving to be a versatile tool to study protein-protein, protein-nucleic acid, protein-lipid, enzyme-substrate, and protein-drug interactions (129).

6. SINGLE CELL PROFILING

The isolation and characterization of homogeneous cell populations or limited number of cells are of great importance in complex diseases when the tissue of interest is limited or when the study is on selective cells (130). Laser microdissection (LCM) can isolate tissues (cells) or even one cell of interest without contamination from surrounding tissues (131). Combining this technology with RNA amplification methods such as exponential polymerase-chain reaction (PCR) based analyses, linear RNA amplification including amplified antisense (aRNA) RNA amplification and a newly developed terminal continuation (TC) RNA amplification enable the use of microarray platforms in restricted number of cells (132). By combining laser microdissection and subsequent microarray technology, several studies have resulted in the identification of disease-related genes including carcinomas and adenomas (133), neoplastic and non-neoplastic prostate tissue (134), and Langerhans cells (135).

7. TISSUE PROFILING

Tissue Microarray Analysis (TMA) is commonly used in development of diagnostic and prognostics markers for clinical applications in addition to confirming results of expression and protein microarrays (136). The manufacturing process is as follows: tissues embedded in paraffin block are cut by cylinder and transferred into a new paraffin block side by side. The new tissue section is transferred onto a slide. A TMA slide can be processed like an ordinary tissue section, and used for histochemical, immunohistochemical staining or in situ hybridization. These slides can be used for genomic and proteomic research for protein or gene localization and verification of microarray experiments or protein arrays. Combined with automated new image analysis systems, TMAs are a powerful molecular profiling tool. Up to 500 tissues can be tested in a uniform standardized, rapid, and cost-effective experiment and screening procedures (137). Such studies have been implemented in endometrial cancer (138) prostate cancer (139) Breast cancer (140). It is projected that TMAs will lead to rapid application of basic research findings into clinical applications (141).

8. INTEGRATION

Global genetic analyses, through a variety of microarray techniques, permit comprehensive interrogations of a multiplicity of genetic and genomic variables. Several studies have utilized a combination of microarray applications demonstrating the power of such approaches. For example, to assess effects of epigenetic treatments (gene expression, DNA methylation, and histone acetylation) in parallel Shi et al. used an integrated microarray panel consisting of 1507 short CpG island tags located at the 5'-end regions on a human epithelial ovarian cancer cell line (142). In addition, simultaneous gene expression analysis and genotyping achieved by combining microarray expression data with publicly available SNP genotype data allowed Morley et al. to identify numerous transcriptional regulatory loci, without any prior knowledge of the regulatory mechanism (143). Finally, Nigro et al. integrated array-comparative genomic hybridization and array-based gene expression profiles to identify relationships between DNA copy number aberrations, gene

expression alterations, and survival in glioblastoma patients. This study indicates that integrating DNA and mRNA-based tumor profiles offers the potential for a clinically relevant classification more robust than either method alone and provides a basis for identifying genes important in glioma pathogenesis (144).

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