

# An array of insights: application of DNA chip technology in the study of cell biology\*

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**The advent of DNA microarray technology has ushered in an era of systems biology whereby researchers can study the transcriptional behavior of thousands of genes in parallel. Advances in manufacturing techniques and informatics, and the availability of several genome sequences have furthered these capabilities to the point where whole-transcriptome studies can be accomplished in yeast, flies and plants, and soon will be possible in mammals. Concomitant with the expanding ability of the technology has been the development of novel techniques and their application towards the study of cellular biology.**

Recent years have seen an exponential rise in the number of studies that have used DNA chip technology to study cell biology. Built around the basic principles of nucleic acid hybridization [1], their most prevalent use so far has been the detection of steady-state mRNA expression. These applications include basic molecular annotation (e.g. Where is my gene? When does it change? Which other genes change?), discovering disease markers and advancing the prediction of clinical outcome, as well as a growing role as the tool of choice for studying transcriptional output. New applications such as genomic DNA analysis to detect DNA synthesis, recombination and chromosomal duplication and loss, as well as combined chromatin immunoprecipitation and microarray chipping approaches to identify transcription factor-binding sites, are being developed and will enable other areas of biology to be explored in this same, highly parallel manner. Finally, alongside sequence query tools, the standardization of data formats and new display and query tools will further both the penetrance of these techniques and their applications in molecular biology.

Because excellent descriptions of the methodologies, platforms for DNA microarray technologies and publication formats are available elsewhere (e.g. see [2–4]), this review focuses on the use of these technologies towards a better understanding of cell biology (outlined in Fig. 1).

## Use of arrays in the study of mRNA expression

DNA arrays have been classically used for investigating the effect of a given biotic or abiotic perturbation on the

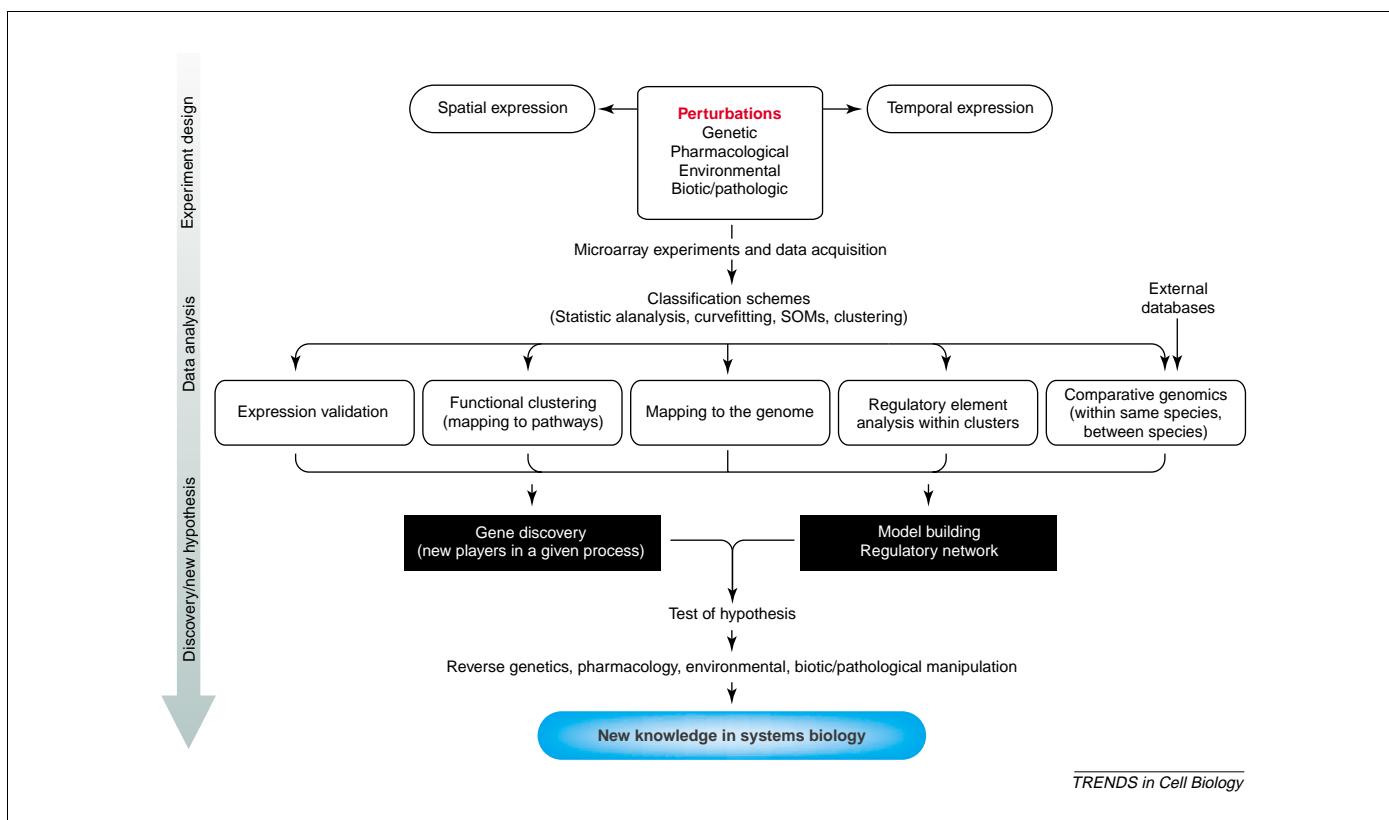
transcriptional output of a system. Underlying these experiments is the notion that analyzing the response of a system to a given perturbation can shed light on the mechanism of signaling or the biological response to the perturbation, or both. One of the best examples of a systematic genome-wide study comes from yeast, for which more than 20 different genetic and growth condition perturbations have been analyzed and used to construct the galactose utilization regulatory network [5]. Using DNA microarrays and quantitative proteomics, changes in the expression of mRNA and protein in yeast in response to each of the conditions were measured. These mRNA and protein expression data, along with data on protein–protein interactions, were used to construct a metabolic regulatory network that confirmed many known regulatory mechanisms and uncovered several putative regulatory steps.

A separate systematic study in *Arabidopsis* has identified a transcriptional network underlying a plant's response to pathogens [6]. Infection with avirulent pathogens elicits a broad-spectrum 'systemic acquired resistance' throughout the plant, which requires the accumulation of salicylic acid and is marked by activation of a set of 'pathogenesis-related' (PR) marker genes. Transcriptional profiling of *Arabidopsis* plants under more than a dozen conditions of genetic perturbation and microbial challenge identified a large cluster of genes that are coexpressed with *PR-1*. Promoter analysis of these putative key mediators of systemic acquired resistance identified an over-represented W-box motif TTGAC, which is a binding site for transcription factors of the WRKY class.

In certain areas of biology, such as development, aging, the cell cycle and biological rhythms, experiments based on temporal gene expression profiling have advanced our understanding of these processes. The cell cycle [7–9] and circadian rhythms [10–13] represent some of the best examples of successful temporal expression profiling, in part because of the powerful application of curve-fitting techniques and repeating patterns. In many independent studies, hundreds of transcripts have been found to show rhythmic expression patterns in their steady-state message levels, with a periodicity very close to that of the cell cycle (e.g. see [7]). These transcripts have been classified into separate clusters on the basis of the stage of the cell cycle corresponding to the peak phase of expression. *In silico* analysis of the promoter elements of these gene clusters has identified over-represented 5' motifs, many corresponding to binding sites for known transcription

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**Fig. 1.** DNA microarrays in systems biology. A typical microarray experiment is designed to measure the spatial and/or temporal expression pattern of genes in a specific set of conditions. After data acquisition, analysis is done to identify those genes that change informatively in an experiment. Expression changes can be validated, and the genes themselves can be mapped to biological pathways or the genome, used for regulatory element analysis or even analyzed across model systems. Several analysis strategies can be used to identify genes in a given process and/or to model regulatory networks. The adoption of standards in data formatting and annotation, as well as new databases to disseminate gene expression information, will facilitate analysis within and across different species. Models and/or hypothesis built on microarray experiments are eventually tested by conventional approaches to ultimately generate new knowledge in systems biology.

factors and some corresponding to previously unknown motifs, suggesting the involvement of additional transcription factors in regulating the cell cycle.

A comparison of gene expression patterns between wild-type yeast and a strain containing null mutations in two members of the highly conserved family of forkhead transcription factors revealed their roles in regulating the cell-cycle-dependent expression patterns of genes important for mitosis [14]. A similar study on the circadian system in *Arabidopsis* identified hundreds of genes showing rhythmic expression patterns in their steady-state levels of mRNA [12]. Analysis of the promoter regions of clusters of genes cycling in the evening phase identified an over-represented *cis*-acting 5' motif, which is very similar to the binding site for transcription factors containing a Myb domain in mammalian cells. Genetic disruption of this motif was found to abolish rhythmic expression, thereby establishing that this *cis*-acting element has a crucial role in regulating circadian gene expression.

Collectively, these studies underscore the power of combining large-scale, parallel, experimental approaches such as DNA arrays with computational and validation tools.

### Microarrays in the study of human disease

An increasingly popular application of DNA arrays is in the study of human disease. The central goals of these studies have been the early detection of disease pathology, diagnosis including class and outcome prediction, and the

identification of causal disease genes themselves. For diagnostic markers of human diseases such as cancer, clinicians have traditionally relied on altered expression levels of serendipitously discovered genes and proteins. For example, increased serum levels of prostate-specific antigen (PSA) have long been used as an indicator for prostate cancer, and overexpression of the tyrosine kinase growth factor receptor, Erb-B2, has been linked to breast cancer. Typically, however, such markers are limited: increased serum PSA can also result from benign diseases, and overexpression of Erb-B2 occurs in only a fraction of all breast tumors and is not completely predictive of an individual's response to Erb-B2 antagonists such as herceptin. Thus, genomic and bioinformatic approaches based on microarrays can be used to supplement existing tools to produce more accurate diagnoses.

Proof of principle that these methods can identify disease-specific markers comes from the study of two types of acute leukemia: acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). Both of these disorders are treatable by traditional chemotherapy; however, successful treatment is largely dependent on correct diagnosis. To find a distinct molecular signature for these two diseases, oligonucleotide microarrays were used to identify a set of 50 genes that can differentiate between AML and ALL with great accuracy [15]. These methods have also been extended to the analysis of several classes of tumor. For example, Su *et al.* [16] have established a list

of about 110 genes that are highly characteristic and therefore diagnostic of colon, bladder, kidney, liver, pancreas, ovary, prostate, lung, gastric and breast cancers.

More recently, it has been possible to show that these methods can be applied to predicting disease outcome. Some individuals affected with ALL also have a chromosomal translocation in the mixed-lineage leukemia (*MLL*) gene. Unfortunately for these people, this additional translocation is linked to relapse after chemotherapy and a poor prognosis for survival. Array profiling of leukemic cells taken from individuals with ALL or ALL/*MLL* identified a predictor set of 100 genes with expression patterns that can differentiate between ALL and ALL/*MLL* [17]; in addition, this profiling highlighted the marked changes in gene expression that can occur with chromosomal translocations. It is important to note that there are many remaining challenges involved in translating these techniques from the research laboratory to the clinic. The potential benefits that they facilitate, however, warrant the considerable attention that these studies have received.

Applying DNA chip technology to experiments aimed towards our understanding of disease causality has proved more difficult. When coupled with transgenic model organisms, however, microarrays can provide valuable mechanistic insight into human disease. Microarray comparisons between poorly metastatic and highly metastatic melanoma lines isolated by *in vivo* selection in mice detected a strong correlation between the severity of tumor metastasis and expression of the small GTPase RhoC [18]. In follow-up experiments, overexpression of RhoC alone in weakly metastatic melanoma cells enhanced metastasis in the mouse. Thus, through microarrays, a putative causal role for RhoC in the development of metastases has been identified.

DNA microarrays have also been used to identify contributing factors in the development of the neurological disease multiple sclerosis, by determining changes in gene expression in the brains of rats with experimentally induced autoimmune encephalomyelitis (EAE) – the best-characterized animal model for multiple sclerosis [19]. This analysis identified increased expression of the pro-inflammatory cytokine, osteopontin, which has been found to be also overexpressed in the brain lesions of individuals affected with multiple sclerosis. Investigation of osteopontin-deficient mice revealed a requirement for osteopontin in the normal progression and maintenance of EAE. From the initial microarray profiling of disease states, genes found to be differentially expressed such as osteopontin and RhoC could serve as drug targets, whose inhibition might provide relief for the many people afflicted with devastating diseases such as cancer and multiple sclerosis.

### Gene annotation

One of the most basic uses of arrays in the study of cell biology is the annotation of gene function by mRNA expression. After a new gene has been cloned, basic characterization has traditionally included the analysis of mRNA expression by a multiple tissue northern blot, which is sometimes followed by higher-resolution

techniques such as *in situ* hybridization. In addition to providing valuable information confirming the size and nature of transcripts derived from a structural gene, implicit in these studies has been the idea that understanding where and when a gene is expressed sheds light on its physiological function.

The recent sequence assembly of mammalian genomes and subsequent efforts at gene prediction has highlighted the need for a higher-throughput approach towards expression annotation. For example, we and others have looked at the expression of thousands of transcripts from the mouse across 50 types of tissue, gaining insight into global patterns of transcription and at the same time making this information available in publicly available databases (see [20]).

New methods to predict genes *in silico*, and the application of these methods to several recently solved genome sequences, have brought about another use for mRNA expression – that is, transcript validation [21,22]. This method has several advantages over the use of expressed sequence tag sequences to quantify gene expression, not least of which is that it can be directed to any particular target sequence and thus can be used to validate the expression of hypothetical, predicted genes.

### Transcriptional output and mechanism

An obvious use for DNA arrays is in the study of transcriptional output. By relating transcription factors to the output genes that they regulate, it is possible to construct transcriptional regulatory networks that link key factors to the biology that they control. By characterizing transcription factor deficiency and overexpression in cell lines and mice, several groups have begun to describe such networks. For example, oligonucleotide microarrays have been used to compare the transcriptional readouts of wild-type and transgenic mice with a null mutation in *TAF<sub>II</sub>105*, a gene encoding a cell-type-specific component of the RNA polymerase II transcription factor TFIID [23]. The expression of genes from the inhibin–activin–follistatin folliculogenesis pathway are markedly down-regulated in the mutant strain, explaining the defects in ovarian development and fertility found in *TAF<sub>II</sub>105* knockout mice.

This microarray analysis of transgenic organisms has not been limited to knockout strains. Specific activation of the forkhead transcription factor FOXO3a in rat fibroblasts was found to induce the expression of genes involved in cellular responses to stress [24]. One such gene, Gadd45a, has been characterized further, identifying a role for FOXO3a in the transcriptional regulation of DNA repair pathways.

### Expanding uses and emerging possibilities

Above we have discussed the use of DNA arrays primarily in mRNA profiling experiments and also several of the ways in which they are being used to study cell biology. Recently, however, researchers have been using arrays to explore other areas of cell biology in the same, highly parallel, experimental manner (summarized in Fig. 2). For example, the sensitivity and accuracy of microarray hybridization have been applied to studies of the replication

dynamics of the yeast genome. By comparing changes in DNA copy number at thousands of sites across the genome during progression through S phase, the sites of origin of replication were identified [25]. The temporal distribution of origin activation, rates of replication fork movement across the genome, and the relationship between replicating DNA and transcription during S phase were also explored.

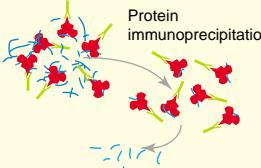
This genomic DNA hybridization technique has also been used in conjunction with traditional mRNA hybridization to investigate meiotic transcription in budding yeast. Primig *et al.* [26] compared meiotic gene transcription in two yeast strains and described considerable differences in the underlying genomes, including polymorphisms and deletions, as well as resultant differences in mRNA expression patterns. Comparative genomic DNA hybridization has found an increasingly popular use in genome-wide scans for changes in DNA copy number. Such studies on hundreds of types of tumor have identified novel gene amplifications (see [27,28] for examples; reviewed in [29]). Arrays have also been used to interrogate targets of RNA-binding proteins. For example, in an effort to identify mRNA-binding targets of fragile X mental retardation protein (FMRP), Brown *et al.* [30] immunoprecipitated FMRP and probed microarrays with the mRNA that co-immunoprecipitated (Fig. 2). Half of the immunoprecipitated mRNAs were found to be translated abnormally in cells from individuals affected with fragile X and, notably, many of these mRNA species correspond to genes implicated in neuronal function and development.

Arrays are also being used to construct transcriptional networks by monitoring the binding of transcription factors

to yeast genomic DNA directly [31]. This method uses chromatin immunoprecipitation (ChIP) as a powerful method to detect physical interactions between known proteins and their DNA target sites. Instead of sequencing immunoprecipitated target genes, however, Ren *et al.* [31] used DNA arrays to deconvolute the target identities. They describe the use of this technique, 'ChIP-chip', for the characterization of two transcription factors involved in carbon utilization and mating, thereby identifying several known and unknown target genes.

In an independent study, ChIP-chips were used to also identify unknown origins of replication by immunoprecipitation of Orc1, the complete ORC complex, as well as Mcm3, Mcm4 and Mcm7. These proteins are known to bind DNA and to function in the formation of origins of replication [32]. In addition, investigations with ChIP-chips have also led to significant understanding of how transcription factors control specific processes and transition stages of the yeast cell cycle. With this method, it was found that stage-specific cell-cycle transcription factors often control the expression of transcription factors that regulate the next stage, revealing mechanistic insight into the continuous transcriptional coordination of the cell cycle [33]. Furthermore, ChIP-chip analysis has identified distinct functional gene clusters (e.g. groups of genes involved in DNA synthesis or repair) that are controlled by specific cell-cycle transcription factors [34].

The use of ChIP-chips has not been limited to studying DNA-binding transcription factors and can be used to delineate the functions of histone modification and mRNA-binding proteins. Chromatin remodeling by

Substrate			
Sample labeling			
Hybridization to microarray of probe sets for	Transcribed and/or untranscribed DNA	mRNA	DNA or RNA
Readout	DNA copy number at thousands of sites across the genome	Detection and quantification of thousands of RNA Pol I generated transcripts	Binding sites for DNA binding proteins or protein bound RNA
Interpretations	<ul style="list-style-type: none"> <li>• Aneuploidy</li> <li>• Gene amplification</li> <li>• Replication dynamics</li> <li>• Polymorphism detection</li> <li>• Recombination break point map</li> </ul>	<ul style="list-style-type: none"> <li>• Spatial gene expression patterns</li> <li>• Temporal gene expression patterns</li> <li>• Transcriptional network construction</li> </ul>	<u>ChIP</u> <ul style="list-style-type: none"> <li>• Transcriptional network construction</li> <li>• Binding sites for proteins involved in genome maintenance and replication</li> <li>• RNA binding protein immunoprecipitation</li> </ul> <u>• RNA binding protein targets</u>

TRENDS in Cell Biology

**Fig. 2.** Current applications for DNA microarrays. Classical microarray experiments use isolated genomic DNA or mRNA from a whole organism or tissue. The DNA or mRNA is transformed and amplified into fluorescently labeled cDNA or cRNA, respectively, which is then hybridized to microarrays. These types of experiment have been used to identify changes in DNA copy number and mRNA expression patterns. Recent innovations in microarray approaches have used an additional purification step by protein immunoprecipitation to identify DNA (chromatin immunoprecipitation or ChIP) or mRNA-binding proteins. Protein bound to DNA or mRNA is first crosslinked and then immunoprecipitated by an antibody to a specific protein of interest. Crosslinks are then reversed, which releases the co-purified DNA or mRNA for amplification, labeling and hybridization to microarrays. These procedures have been successful in determining the targets of transcription factors, as well as genomic DNA-binding and mRNA-binding proteins.

histone acetylation/deacetylation has emerged recently as a chief regulatory mechanism of gene expression. Gene targets of yeast histone deacetylases (HDACs), which antagonize chromatin remodeling and gene expression, have also been identified by using ChIP-chips [35]. This study also showed that HDACs display target-site specificity for their action. Thus, ChIP-chip is emerging as a powerful tool for the exploration of protein–DNA interactions and its use should provide fertile ground for the growth of whole-genome transcriptional networks.

### Concluding remarks

DNA arrays and the parallel biology that they empower have pushed experimental approaches to genome-wide and whole-system levels. Their use in the study of mRNA expression and transcriptional regulation has been adopted widely by the research community for exploring virtually every area of biology. Despite many successes, however, difficult challenges remain. Importantly, one should have realistic expectations for the application of DNA arrays, because many problems in cell biology cannot be addressed by looking at transcriptional responses or signatures.

Technical limitations currently prevent higher-eukaryotic transcriptomes from being analyzed in a whole-genome fashion. Current sample preparation methods require relatively large quantities of RNA, which limits studies on discrete cell types in complex structures, such as small nuclei in the brain. The cost and infrastructure required for array experiments remain a significant entry barrier for many laboratories and can result in studies with less than satisfying experimental and statistical designs. Current methods to analyze, visualize and disseminate data are sometimes cumbersome, expensive or piece-meal, and have not yet been standardized to facilitate the exchange of data and results between researchers.

Although these problems are significant, current efforts to address these and other issues involved in DNA array experiments will undoubtedly improve on current circumstances and will translate into many future discoveries in cell biology. The adaptation of DNA arrays to other highly parallel, experimental approaches such as ChIP-chip, RNA binding and comparative genomic DNA hybridization has enabled other areas of cell biology to benefit from the same comprehensive advantages. The further development of these techniques and other parallel approaches to cell biology (e.g. see [36,37]), as well as the emergence of data standards [3] and computational and visualization methods, will continue to transform the process of experimentation from the study of a single gene in a single process to a whole-genome approach.

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