Biomedical Science Letters 2014, 20(4): 185~193
http://dx.doi.org/10.15616/BSL.2014.20.4.185
eISSN : 2288-7415

Review

Microarray Approaches in Clinical Oncology: Potential and Perspectives

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Cancers are based upon an array of orchestrated genetic changes and the identification of changes causally related to the carcinogenic process. To elucidate the mechanism of cancer carcinogenesis, it is necessary to reconstruct these molecular events at each level. Microarray technologies have been extensively used to evaluate genetic alterations associated with cancer onset and progression in clinical oncology. The clinical impact of the genomic alterations identified by microarray technologies are growing rapidly and array analysis has been evolving into a diagnostic tool to better identify high-risk patients and predict patient outcomes from their genomic profiles. Here, we discuss the state-of-the-art microarray technologies and their applications in clinical oncology, and describe the potential benefits of these analysis in the clinical implications and biological insights of cancer biology.

Key Words: Microarray technologies, Cancer cytogenpetics, Copy number variations

1. Introduction

Cancer involves complex combinations of molecular events, such as genetic aberrations, epigenetic changes, and alterations in gene expression. The remarkable progress in the understanding of carcinogenesis has been spurred by methodological developments in cytogenetics (Varella-Garcia M, 2003).

Microarray technology represents the technical convergence of molecular genetics and cytogenetics, and is rapidly revolutionizing modern cytogenetics (Maciejewski JP and Mufti GJ, 2008). Genomic analyses using microarrays have been successfully used for cancer stratification into molecular subgroups with relevant implications for clinical outcomes, therapeutic targets and detection of prognostic/ treatment predictive signatures (Fig. 1).

*Received: July 17, 2014 / Revised: September 1, 2014
Accepted: September 27, 2014

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Although commercially available arrays have proven to be an indispensable tool for diagnosing patients with intellectual disabilities and/or multiple congenital abnormalities, it has been more challenging to implement the technology in the diagnostic cancer genetic setting. Nevertheless, array-comparative genomic hybridization (CGH) or single nucleotide polymorphism (SNP) arrays have been shown to be a cost-effective alternative to multiple fluorescence in-situ hybridization (FISH) testing to identify genomic imbalances.

A large number of studies utilizing the microarray technologies in cancer research have produced a wealth of useful information about copy number variations (CNVs) (Kallioniemi A, 2008; Simons A et al., 2012). These studies have highlighted the overall patterns of copy number aberrations in clinical oncology and have identified in high-resolution specific genetic alterations associated with certain tumor entities, cancer classification, disease progression, therapy response, and patient outcome (Kallioniemi A, 2008). Consequently, array-based technologies are slowly but surely finding their way into the clinical laboratories for cancer cytogenetics.

This review presents an overview of the clinical value of microarray technologies in cancer cytogenetics and discusses

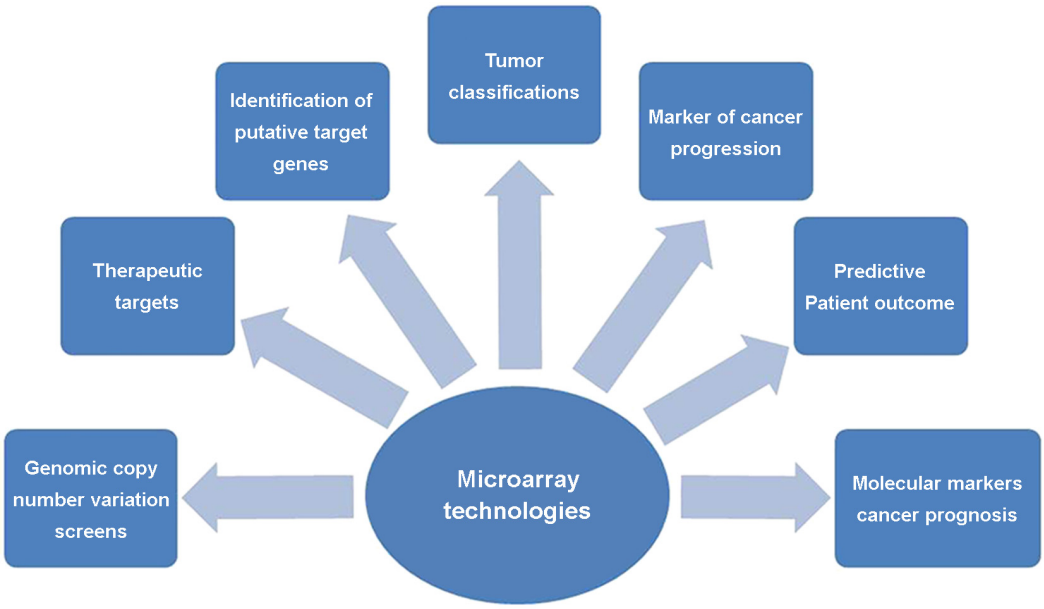

Fig. 1. The schematic overview of the applications of microarray technologies in clinical oncology.

current uses and outlines potential applications of these assays in clinical oncology.

2. Routine Cytogenetics Diagnostics and Limitations in Oncology

Cytogenetic investigations have provided fundamental insights into the molecular mechanisms of cancer genetics. A wealth of cytogenetic data has demonstrated that numerous somatic genetic changes are involved in cancer genetics. Cytogenetic analysis of cancer has become an integral part of disease evaluation and prediction of prognosis or responsiveness to therapy.

Conventional cytogenetic methods, such as karyotype investigation, have proven fundamental for initial discoveries concerning the molecular mechanisms of carcinogenesis, and have become recognized as the gold standard for the detection of copy number imbalance across the genome. However, conventional karyotyping is relatively costly due to its laborious nature; it also has technical limitations, and many potentially clinical relevant submicroscopic chromosomal abnormalities remain undetected (Simons A et al., 2012).

The advent of molecular cytogenetic strategies, such as multiplex FISH (M-FISH), spectral karyotyping (SKY) and CGH have increased the accuracy of identifying chromosomal rearrangements. It has repeatedly proven effective in genetic diagnostics and has been recognized as a valuable addition or even alternative to chromosomal banding analysis (Kang JU et al., 2006). In most diagnostic laboratories, conventional karyotyping, in conjunction with targeted FISH analysis, is routinely performed to detect recurrent aberrations with prognostic implications.

The cytogenetic component of this continuum has fulfilled much of its pioneering role and now constitutes a small but dynamic segment of the vast literature on cancer genetics, in which it has played an important if not initiating role (Sandberg AA and Meloni-Ehrig AM, 2010). However, the level of resolution (5~10 megabases) of these methods in cancer cytogenetics is not fine enough to be used for positional cloning of genes at chromosomal breakpoints or those tumor suppressor genes mapping to regions subjected to deletion (De Braekeleer E et al., 2011). Additionally, all experiments are labor-intensive and time-consuming, especially when multiple genomic regions are interrogated. Therefore, it is strongly advised to investigate these rear-

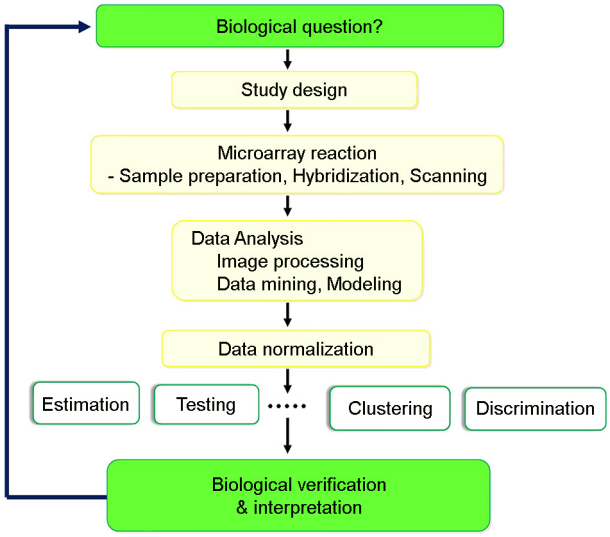

Fig. 2. Block diagram of the microarray life cycle. Shown are the six steps of microarray experimentation: step 1, biological question; step 2, study design; step 3, microarray reaction; step 4, data analysis; step 5, data normalization; step 6, biological verification & interpretation.

rangements with higher resolution and excellent throughput.

3. Microarray-based Cytogenetic Technology

Microarray techniques provide a platform where one can measure the expression levels of tens of thousands of genes in a sample. Various DNA array-based assays have been introduced to facilitate the examination of cancer genetics. Based on the availability of bacterial artificial chromosome (BAC) libraries, arrays with various densities of BAC probes have been generated, enabling array-based CGH.

The subsequent introduction of high-density oligonucleotide arrays has enabled even more precise scanning of the genome for copy number changes. Using a similar microchip technology, SNP arrays developed for whole genome association studies, have also been adopted for karyotyping (Maciejewski JP et al., 2009). Several commercial array platforms offer the combination of probe designs, covering hundreds to thousands of cancer associated genes and allowing the detection of even single exon deletions or duplications of selected genes known to be important prognostic genetic markers (Simons A et al., 2012) (Fig. 2).

New array design will continue to improve resolution and detection sensitivity, while more efficient production strategies and streamlined experimental protocols will reduce cost and effort requirement. In addition, the emergence of new software aiming at automating breakpoint detection and statistical analysis will simplify the daunting task of the interpretation of array profiles data sets. The continuing technical advances and growing databases of disease-specific profiles will broaden the use of these technologies in both cancer research and clinical settings (Lockwood WW et al., 2006).

4. Clinical Application of Microarray Technologies in Oncology

Cancer is a genetic disease of somatic cells arising from accumulation of genetic changes, and abnormalities of suppressor genes and oncogenes are frequently associated with carcinogenesis (Midorikawa Y et al., 2007). Discovery and functional assessment of cancer related genes is essential for understanding the biology of cancer and for clinical applications, including identification of subgroups with relevant implications for clinical outcomes, therapeutic targets, and molecular markers for cancer prognosis and the prediction of treatment response.

Microarray technology is a versatile platform that allows rapid genetic analysis to take place on a genome-wide scale, and has revolutionized to evaluate genetic markers and changes in cancer genetics. Information derived from these assays allows clinicians to estimate the risk for distant recurrence, and predict accurately which patients are likely to benefit from adjuvant therapy (Cavallaro S et al., 2012).

1) Cancer classification by microarrays

Previous genome-wide analyses have indicated that different tumor types typically possess more or less specific sets of genetic changes. For instance, it has been proposed to be routinely used to stratify the disease into clinically relevant subgroups, with implications for the prognosis and treatment of cancer. In a seminal study, Perou et al. (Perou CM et al., 2000) distinguished different subtypes of breast cancer based on their gene expression profiles and Waddell

et al. (Waddell N et al., 2010) identified regions of frequent gain containing potential driver genes in the basal (8q and 12p) and luminal A tumors (1q and 17q) in familial breast tumors. Distinct spectra of CNVs underlie different subtypes of breast cancer as also defined by expression-profiling (Bergamaschi A et al., 2006; Vincent-Salomon A et al., 2008). Similarly, hereditary *BRCA1* and *BRCA2* breast tumors develop by specific and distinct evolutionary paths, as their gene expression profiles and genome aberration spectra differ from each other and from those in sporadic breast tumors (Wessels LF et al., 2002).

Furthermore, in a study of gastric adenocarcinoma, the genomic profiling of CNVs has allowed discrimination of a subgroup of patients with high risk of lymph node metastasis and is predictive of prognosis (Weiss MM et al., 2003). Recurrent CNVs differ between tumor subtypes defined by expression pattern and stratification of patients according to outcome can be improved by measuring both expression and copy number, particularly high-level amplification. These analyses have confirmed that tumor type specific copy number patterns do exist and can be used for efficient tumor classification.

Additionally, to specifically explore the utility of copy number patterns for tumor classification, Jong *et al.* (Jong K et al., 2007) performed a meta-analysis combining array CGH data from 373 primary tumors obtained using three different array platforms (bacterial artificial chromosome (BAC), cDNA, and oligo) in four different institutes. Importantly, no platform or institute specific patterns were highlighted suggesting that copy number data derived from different laboratories using different array formats can indeed be easily merged. Clustering analysis revealed that tumors were separated, not only according to their tissue of origin but also according to their embryonic origin (Carrasco DR et al., 2006).

Moreover, genomic copy number profiles have been used to distinguish distinct subgroups within histologically defined disease entities (Alizadeh AA et al., 2000; Martinez-Climent JA et al., 2003; Weiss MM et al., 2004; Rubio-Moscardo F et al., 2005; Carrasco DR et al., 2006; van Beers EH et al., 2006; Kang JU et al., 2009). In multiple myeloma, unsupervised clustering of array CGH data was able to divide cancer cases into specific subgroups that showed differences in clinical outcomes (Carrasco DR et al., 2006). Furthermore, in a seminal publication, they analyzed the expression of approximately 6,800 genes in bone marrow from 38 patients with acute leukemia with the acute lymphoblastic form, ALL, and 11 with the acute myeloid form, AML. Fifty genes whose levels of expression differed most between AML and ALL cells were selected. Using this subset of genes, the investigators were able to correctly identify patients had AML and which had ALL in a blinded new cohort of 36 patients (Alizadeh AA et al., 2000).

Previously, our own study (Kang JU et al., 2009) successfully identified significant differences and unique information of chromosomal signatures prevalent and related genes involved in different subtypes between the squamous cell carcinoma (SCC) and adenocarcinoma (AC) of non-small cell lung cancer (NSCLC) using whole-genome array CGH. Similar efforts are being made for other tumor types, such as lymphoma (Martinez-Climent JA et al., 2003; Rubio-Moscardo F et al., 2005), gastric (Weiss MM et al., 2004), and prostate cancers (Paris PL et al., 2004). Many more studies are in press or nearing completion. From all these considerations, detailed characterization of genomic changes using microarrays can improve cancer classification and may identify clinically useful subgroups of cancer patients.

2) Genomic aberrations as predictive markers

DNA microarray profiling can also be useful as molecular markers for cancer prognosis or the prediction of treatment response. Currently, several commercial array platforms offer the combination of probe designs, covering hundreds to thousands of cancer associated genes, and allowing the detection of even single exon deletions or duplications of selected genes known to be important prognostic genetic markers.

For example, in the experiment of Ramaswamy *et al.* (Ramaswamy S et al., 2003) 12 metastatic adenocarcinoma nodules of diverse origin (lung, breast, prostate, colorectal, uterus, and ovary) were compared with 64 primary adenocarcinomas representing the same tumor types from different

individuals, forming a training set of 76 samples. The authors found 128 genes differentially expressed between the metastatic and the primary tumors and use these genes to build a predictor that was tested to classify primary tumors of different origins.

Similarly, in diffuse large B-cell lymphoma (DLBCL), authors distinguished two previously unknown groups of DLBCL. The two groups were called "germinal center B-like DLBCL" and "activated B-like DLBCL" because the main differences between them were genes involved in B cell activation and in germinal center formation. These two new taxonomic groups are not only biologically relevant, but they also have an important prognostic value, as the authors showed that 5 years after anthracycline-based chemotherapy treatment, 76% of germinal center B-like DLBCL patients survived, while only 16% of activated B-like DLBCL did (Alizadeh AA et al., 2000).

A similar screen, in head and neck squamous-cell carcinomas, array CGH analysis allowed the identification of CNVs that differ between tumors with or without oncogene-expressing human papillomavirus (Wilting S et al., 2006). Weiss *et al*. also explored the role of CNVs in breast cancer by identifying associations between recurrent CNVs, gene expression, and clinical outcome in a set of aggressively treated early-stage tumors (Smeets SJ et al., 2006). These results indicated that CNVs may provide a basis for improved patient prognosis as well as a starting point to define important genes contributing to cancer development and progression (Chin K et al., 2006).

In 2005, the first pharmacogenetic microarray test was approved by the United States Food and Drug Administration and a commercial product was manufactured by Roche. This test classifies the patient on the basis of SNP profiles of the cytochrome P450 (CYP) genes *CYP2D6* and *CYP2C19* into poor, intermediate, extensive or ultrarapid metabolizers. This information can then be used by the clinicians to adapt the dose specifically for therapeutics that are metabolized by these two enzymes (de Leon J et al., 2006). Additionally, the discovery and approval of targeted therapeutics in lung cancer, such as gefitinib and crizotinib for *EGFR* mutated and *EML4-ALK* translocated NSCLC, respectively, and *BRAF* mutation in melanoma, has shifted the attention from gene expression signatures/studies towards the development of novel therapeutic strategies based on the presence of genomic aberrations (Ruiz C et al., 2012). These findings will potentially aid in the early identification of at-risk individuals and allow earlier detection of cancer, optimizing prognosis and the chance for cure.

3) Identification of putative target genes by microarrays

The ultimate goal of microarray studies is to pinpoint the locations of cancer-associated genes as accurately as possible. In many cases, these aberrations contain known oncogenes or tumor suppressor genes whose expression levels are altered by the genomic changes.

For instance, Pfeifer *et al*. (Pfeifer D et al., 2007) described microduplication encompasses the *REL* and *BCL11A* oncogenes, which have been implicated in CLL pathogenesis. Another experiment using array CGH has also shown that different breast cancers progress along different genomic pathways (*HER2*, *cyclin D*, and 8q and 20q amplifiers) and allowed the identification of novel breast cancer oncogenes within complex amplicons (e.g., 8p12) (Ramaswamy S et al., 2003). Similarly, a combination of CGH with expression profiles has also been used in the case of the 8q11-12 amplicon with the identification of two candidate genes, *FLJ14299* and *SPFH2*, in breast cancer (Ray ME et al., 2004).

Candidate genes searches by microarrays have also included homozygous deletions of established tumor suppressor genes. In the analysis of mantle cell lymphomas identified several regions of homozygous deletions, one of which (2q13) was subsequently shown to target the pro-apoptotic *BIM* gene (Tagawa H et al., 2005). A similar screen in ovarian cancers disclosed a total of 27 homozygous deletions including one corresponding to the well-known *RB1* tumor suppressor gene (Gorringe KL et al., 2007). In the analysis of oral cancers also revealed a homozygous deletion of the *FAT* gene, a member of the human cadherin superfamily (Nakaya K et al., 2007). These examples illustrate that high-resolution microarrays has indeed improved the detection of high level amplification and homozygous deletions in cancer and facilitated the identification putative novel oncogenes and tumor suppressor

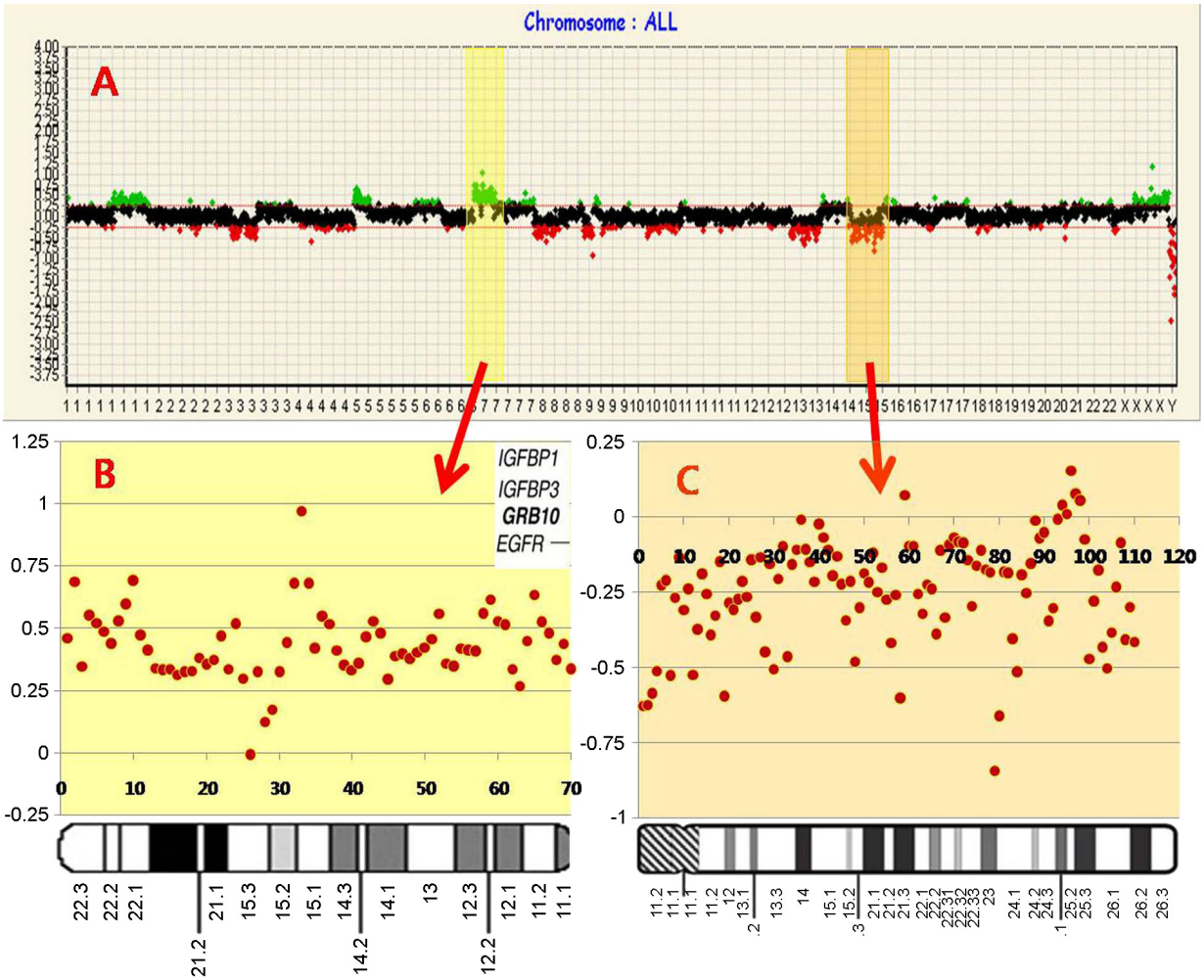

Fig. 3. An example of genomic imbalances detected by an array CGH analysis. (A) Whole chromosome analysis in non-small cell lung cancer showing various copy number alterations. (B) Arrow points to the close-up view of the high level amplifications of short arm of chromosome 7. (C) Arrow points to the close-up view of the copy number losses at 15q.

genes (Fig. 3).

These are just a selected number of recent studies that serve as examples of the potential use of microarrays in cancer research. The variety of applications include screening of cancers for genetic aberrations, searching for genes involved in the carcinogenesis of particular subsets of cancers, analyzing cancers in experimental models to provide more insight into cancer progression, and using diagnostic classification and prognosis assessment (Ramaswamy S et al., 2003). Furthermore, global sharing of the genomic and pathological data that are now accumulating in publicly available databases will aid in better understanding the genetic mechanisms and driving pathogenic abnormalities.

While the current microarray technologies may be too expensive for routine applications with the introduction of massive whole-genome parallel sequencing, complete mapping of the genomic changes in the malignant cells can be obtained (Simons A et al., 2012). The cost of these technologies will probably decrease further with the use of automation and for wider application. Furthermore, the high-throughput nature of this technology combined with the expected plethora of data results in a high opportunity for errors. To ensure the accuracy and reliability of the resulting data, it is essential, therefore, that experiments are tightly

regulated and quality controlled.

Given its excellent performance in detecting genetic abnormalities in cancers, application of microarray technologies to clinical oncology could be a logical approach in an attempt to establish better management of cancer patients (Sato-Otsubo A et al., 2012).

5. Outlook and Concluding Remarks

Microarray technologies are now coming into wide use, but their potential in expanding our knowledge of cancer genomics is clear and will undoubtedly prove to be a key technology leading to better cancer classification, prognosis and outcome prediction. Further investigation and data, particularly from prospective trials, are required to reach a consensus on the optimum configuration of an array in cancer genetics to satisfy the stringent demands of accuracy and reliability in clinical applications.

Acknowledgements

This study was financially supported by the research fund of Korea Nazarene University in 2014.

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