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Role of Microarray Technology in Diagnosis and Classification of Malignant Tumours

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ABSTRACT

Typical cancer research including diagnosis and classification of tumours performed via clinical , cytological and histopathologically methods .However, some cases show diagnostic disturbances due to inadequate clinical information and aberrant histopathological characters which together demonstrated the disadvantages of typical cancer research in the mentioned branches . Recently, development of microarray technology and gene expression profiles emerged for diagnosis and classification of tumours .This technology could overcome some disadvantages of conventional methods of diagnosis and classification and covered some aspects of unresolved tumour's problems. In this review, we focused on recent discoveries in tumour's diagnosis and classification via microarray technology and importance of this technology in cancer research area. Some important types of cancers recently analysed via microarray technology and reviewed in this paper are such as oral cancers, ovarian cancers, colorectal carcinomas, melanomas and prostate carcinoma and breast cancer. Also classification of some tumours using microarray technology discussed here for emphasis the prominent role of microarray technology in cancer research.

Keywords: Microarray technology, Gene expression profile, Cancer research, Diagnosis, classification of tumours.

I. INTRODUCTION

Cancer is the second cause of death which basically is diagnosed using histopathological and cytological techniques .[1] .However , sometimes application of histopathology and cytology show diagnostic disturbances due to inadequate clinical information and aberrant histopathological characters which together demonstrated their disadvantages [2]. Additionally in tumour study and their classification, several molecular diagnosis and observations aided scientists which usually are such as use of diagnosis of tumour biomarkers, genetic mutations and chromosomal variations , looseness of the long arm of chromosome 14 and activation of ***c-kit*** mutation occurred in gastrointestinal stromal tumours, in acute myelogenous leukemia occurrence of gene rearrangement of bcr/abl and its use as biomarkers and so on. [3-6]. Although these diagnostic observations are available but due to inconsiderable number of target tumour markers, molecular diagnosis is not typically accepted for study and classification of tumours. Moreover, most of genetic variations are not adequately specific to precisely diagnose the tumours and encyclopedic mutation databases for the tumours have not been searched. By development of gene expression profiling via DNA micro-array technology and its application in tumour diagnosis and classification, scientists could advance in diagnosis and classification of tumors.DNA –microarray technology has been facilitated several specific diagnostic marks and observations in different type of tumours such as identification of gene subsets by their characteristically expression , in oral cancers, ovarian cancers colorectal carcinomas, prostate carcinomas and melanomas. Moreover, it provides scientists and researchers with molecular classification of soft tissue sarcomas and classification of tumours to determine primary sites in metastatic cancers. DNA microarray also helps in identification of intertumoral variations within the same histologic tumour types .These variations are used for proper molecular classifications and genetic changes evaluations. Gene expression

profiling via DNA microarray also helps successfully in differentiation of Leukemia types and its oncogenetic route for T-cell type. Additionally this technology helps in identification of a subset genes involved in different biological and genetic changes in solid tumours. [2].In this paper we reviewed recent discoveries in cancer research including diagnosis and tumour classification in different types of cancers for the purpose of illustration of prominent role of microarray technology and encourage scientists for application of this technology in their cancer research programs for precise diagnosis and tumour classification.

II. METHODS AND MATERIAL

A. Recent discoveries in cancer research in association with microarray technology

Application of cDNA microarray in ovarian cancer research: Ovarian cancer is one of the most common cause of deaths among the woman .The prognostic factor for this type of cancer is stage of tumour or disease extension at diagnosis .One of the way for treatment of this cancer is its diagnosis at early stage .cDNA microarray technology has facilitated understanding of early stages and exploration of progression steps in ovarian carcinogenesis .Scientists have applied combined genetic methods for analysis of 21 early tumour stage and 17 late stage in ovarian cancer .These applied techniques included expression profiling with cDNA microarrays consisted of approximately 18,000expressed sequences and comparative genomic hybridization for finding chromosomal loci of copy number for both gain and loose conditions. The result has demonstrated the exhibition of profound alternations of early stage ovarian carcinogenesis in gene expression which showed similarity to those detected in late-stage tumours. However, observation of differences at genomic level proposed differences between the two stages and accommodate a base for a promotion model for development of ovarian cancer [7].

Oral cavity cancer analysis via microarray contribution: Scientists carried out a large scale expression profiling using high-density oligonucleotide microarrays for analysis tumor oral epithelial cells. In this analysis research approximately 600 genes were identified in association with oral cancer. These genes include tumor suppressors, oncogenes, transcription factors, metastatic proteins, differentiation markers, xenobiotic enzymes, and non –implicated genes in oral cancer. This created database serves as a valid comprehensive profile of gene expression for analysis of oral carcinogenesis reporting the significant role of recognized genes as well as and non –implicated genes in oral cancer. In this study, scientists demonstrated the LCM application for harvesting of tumor and normal cells from a solid tumor site of oral cavity cancer type. Linear amplification of mRNAs carryout out by three rounds of T7 RNA polymerase reaction, then biotinylation is done and subsequently hybridization to HuGeneFL-microarrays performed.[8].

Contribution of microarray to identification of genes associated with human melanoma: The need for identification of new molecular markers for diagnosis and analysis of progression stage of melanoma come from the fact that the typical treatment and diagnosis methods are not effective and not completely responsive. Recently, scientists has been developed a new technique for screening of expression of thousands of genes at the same times via high density oligonucleotide arrays. They have used this technique for comparison of the patterns of mRNA of two human melanoma cell lines which show differentiation in their metastatic behavior. Validation of oligonucleotide array's results carried out by methods of Northern blotting and reverse transcription-polymerase chain reaction (RT-PCR) using eight differentially expressed genes named as transforming growth factor-beta superfamily, tyrosinase-related protein 1, , alpha2-macroglobulin, human cell division cycle 10 and serine/threonine protein kinase (DYRK1A), apolipoprotein CII, subtilisin-like protein, elongation factor 1 alpha2. Finally their data and results demonstrated the reliability and accuracy of the high density oligonucleotide arrays for screening for differentially expressed genes in melanoma .This study may be considered as a fundamental step in the identification of malignant melanoma associated genes .[9].

*Revealing of alterations of gene expression in colorectal carcinogenesis by cDNA microarrays***:** Recently scientists identified a set of genes implicated in the progression of colorectal carcinogenesis. They used a DNA microarray including 9216 human genes for comparison of expression profiles of colorectal

cancerous cells from 8 tumors with analogous non-cancerous colorectal cells. Laser-capture microdissection has been applied to this cell community for rendering homogenous. The researchers observed expression change for 235 genes including 191 down - regulated and 44 up-regulated genes in more than half of the tumors .The genes which differentially expressed showed association with metabolizing enzymes, signal transduction, production of reactive oxygen species, mitosis, cell cycle and apoptosis. Their analysis examination provided a reliable and valuable database for colorectal carcinogenesis and provide a strong source of novel target for cancer treatment.[10-11]

Aid of microarray technology in identification of potential markers and pharmacological targets in prostate cancer: Recently, researchers monitored expression levels of more than 8900 genes in normal and cancerous prostate cells in order to characterize primary prostate cancer. By analysis gene expression patterns , they revealed a precise difference between normal and tumor cases and also found a remarkable group of about 400 genes that showed overexpression in tumor tissues . their research and analysis provided identification of prostate implicated genes and their act association with a various biochemical pathways and encoding secreted molecules with diagnostic possibility, such as , MIC-1 and the secreted macrophage inhibitory cytokine, and detection of some genes like fatty acid synthase encoding enzymes which serves as drug targets in other contexts which all together provided new therapeutic approaches. [12-13]

Breast cancer research via microarray technology: Due to scant numbers of precise predictive and prognostic factors which are clinically and histopathologically identified and the need of high throughput technology in breast cancer researches for overcome such disadvantages, DNA microarray has taken a place in breast cancer research for assessment of the expression of thousands of genes simultaneously as well as rapidly. Gene expression profiling provided identification of prognostic gene sets that facilitate prediction of a short intervals to remote metastases.[14]. Using microarray technology study of epigenetic mechanism of tumorigenesis is provided which is helpful in management of cancer. Recently scientists identified changes in genome-wide DNA methylation in a breast cancer metastasis using a cell-line miodel. They analyzed complicated epigenetic changes and karyotype which leaded to establishment of hypothesis that multiple genomic changes such as translocations, deletions and ploidy in breast cancer cells are overlapped to over promoter-specific methylation conditions that are involved in gene-specific expression alternations occurred in breast cancer metastasis. Scientists carried out high resolution, whole-genome analyses of MDA-MB-468GFP and MDA-MB-468GFP-LN human breast cancer cell lines simultaneously using combination copy number variant/single nucleotide polymorphism microarrays. Their approach facilitated more precise profiling of functionally related breast cancer associated epigenetic signatures.[15]

B. Role of microarray in molecular classification of cancers:

Although classification of cancers has been started over 30 years and its improvement has been seen but still there is no common approach for identification and prediction of new cancer classes for assessment of tumors to already identified classes. Researchers developed a general approach for classification of cancers based on gene expression profiling via DNA microarray. They developed this approach and applied it to human acute leukemias as a test sample. The discovery achieved using this approach was the identification of difference between acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) independent of previous knowledge about their biology. Their approach suggests a generic strategy for discovery and prediction of cancer classes of other types of cancers without knowing previous knowledge of their biology. In another approach, researchers established a project for organ-specific molecular classification of primary lung, ovarian and colon carcinomas. [16].Scientists has been reported gene expression profiles of 154 primary adenocarcinomas of the lung, ovary and colon. They generated general gene expression profiles of 57 lung, 51 colon, and 46 ovary adenocarcinomas using high-density oligonucleotide arrays consisting 7129 gene probe sets, and then using nearest neighbor classification ,their principle component analysis and cross validated prediction analyses carried out . These statistical analyses showed the classification of 152 of 154 of the adenocarcinomas in an organ-specific behavior and determined genes expressed in a putative tissue-specific behavior for each

tumor type. Additionally identification of two tumors, one in the ovarian group and another in the colon group carried out. These two tumors did not integrate to their corresponding organ-specific groups. Their studies suggest the application of gene expression profiles for classification of tumors and determination of organ-specific gene expression profiles and precise molecular diagnosis. [17]. Analysis of patterns of gene expression of soft tissues tumors including fibroblasts, muscle cells, or adipocytes was carried out using cDNA microarrays. In this approach, 41 soft tissue tumors subjected to cDNA microarrays. After analysis of expression patterns of 5520 genes, they carried out separation of tumors into different groups by hierarchical clustering and singular value decomposition. Their results demonstrated that, Gastrointestinal stromal tumours Synovial sarcomas, neural tumours, and a subset of the leiomyosarcomas, exhibited different gene-expression patterns. Liposarcoma, malignant fibrous histiocytoma, , and the other leiomyosarcomas showed molecular profiles that were not previously identified by prediction methods or immunohistochemistry methods . Their studies and results provided a new approach for classification of soft tissue tumors which is not previously carried out via histopathological methods. This approach helps in improvement of histological finding as complementary method for distinction between the tumors. Thus these discussed findings as examples of application and contribution of microarray technology showed its significant role in identification of new cancer associated genes and classification of tumors in distinct groups for better diagnosis and treatment in cancer control programs **.** [18]

III. CONCLUSION

The molecular background of cancers has been revaluated over the past decade. General cancer research mainly bases on clinical, cytological and histopathologically methods but in some cases , due to diagnostic disturbances emerged from inadequate clinical information and aberranhistopathological characters, the need for advanced methods demands. Microarray technology emerged complementary method with providing a enormous source of data on gene expression changes in cancers. Microarray technology has been established a strong tools in unrevealing problems in oncology .The fundamental studies carried out via microarray technology has been promising enough for providing an individualized dimension to cancer therapy .Microarray technology provides identification of cancer involved genes, cancer associated epigenetic signatures, biomarkers, novel targets genetic changes evaluations and classification of tumors in distinct groups for better study and treatment of cancer. Although microarray analysis is a promising diagnostic method for cancer diagnosis and classification, but it is not separated from limitations. The limitations related to this modality are firstly detailed and exact diagnoses of individual tumors by gene expression profiling lonely are not always feasible. This may be due to unavailability of reference database for encyclopedic gene expression for cancer and lack of development of specific biomarker groups for diagnosis of specific-corresponding tumors .Secondly, the gene expression repots exhibit significant variation within the same tumor due to distinct gene expression profiles in the tumor and the different stromal reaction or peritumoral lymphoid condition. Thirdly, early tumor diagnosis is not possible via microarray technology (gene expression profiling). At the present, cancer diagnosis via DNA microarray is feasible only when large amount and large slice of tumor cells are provided. In spite of these drawbacks, microarray is effectively used for diagnosis of tumors and their molecular classification based on and biological and genetic changes.

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