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Research Article

CANCER TREATMENT-TECHNOLOGY OMICS

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ABSTRACT

Cancer is a disease, which explicitly illustrates success, failures and challenges of the modern biomedi - cal research. Technology development has been the driving force of improvements in the cancer treatment. Introduction into clinical practice of genomics, RNA profiling and proteomics technologies have provided a basis for development of novel diagnostic, drugs and treatments. In this chapter, contributions of OMICs technologies to personalization of cancer diagnostic and treatment are discussed. The focus is on technologies that showed capacity to deliver diagnostic that may be used in the clinic as routine tests. Three clinical cases are presented to illustrate already available individualized cancer diagnostic.

KEYWORDS

Personalized cancer medicine, genomics, transcriptomics, proteomics, metabolomics, diagnostic.

INTRODUCTION

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Why OMICS technologies are needed for treatment of cancer? Cancer still kills people. It was easier to send a man in the outer space or to the Moon, than to improve survival of patients having advanced and metastatic cancers. This highlights complexity of cancer as a disease, which is apparently much higher than to build and launch a space rocket. Carcinogenic transformation of cells is accepted as the main cause of cancer [1–4]. Carcinogenic transformation is defined as a number of changes in the cell physiology, which lead to expansion of malignant cells in the body, corrupting the normal physiology, and ultimately killing the person. The key conclusion of more than 50 years of intense studies is that the collected knowledge has not reached the critical mass required to find cure against cancer. The oncogenes and tumor suppressor model has been a great step forward [1–4], but today is clear that carcinogenic transformation of cells is the result of interaction of hundreds molecules. Out of the hundreds of these cancer-promoting genes, RNAs, proteins and metabolites many are the same as they are in the normal cells. It is their corrupted activity, mis-localization, and misplaced interactions that make them tumorpromoting (Fig. 1). This confusion has only underlined complexity of cancer.

A solution to the complexity problem has been proposed by introduction of technologies for comprehensive study of carcinogenesis. These technologies focused on studies of genomic DNA (genomics), RNAs (transcriptomics), proteins (proteomics) and metabolites (metabolomics) [5–7]. Historically, introduction of nucleotide microarrays to study expression of RNA was the first strong contribution to the comprehensive exploration of carcinogenesis [8]. Development of the microarrays was possible due to successes of technologies for synthesis of oligonucleotides and production of cDNA on a large scale and in automated way. A chip-printing technology was another component of the success. Development of sequencing technologies, especial ly of massive parallel sequencing, has given boost to comprehensive studies of genome for the clinical diagnostic [9]. Comprehensive studies of the proteome are still waiting for a wide use of intact protein analysis technology. Current technologies of mass spectrometry, 2D gel and other electrophoresis, or liquid chromatography are not providing quality that is required for full description of the human proteome [10, 11]. However, the situation may change with introduction of ZP-technology [12]. The least deve - loped of the OMICs technologies is metabo lo - mics. The high variability of physico-chemical and structural properties of the metabolites makes it challenging to detect and identify all metabolites by a single technology. Despite all shortcomings, OMICs studies have become essential for success in treatment of cancer, due to their ability to a comprehensive analysis. Therefore, there is no alternative to deve - lopment of fast, reliable, informative and cost-efficient OMICs technologies for diagnostic and treatment of cancer.

Genomics Since the discoveries that the genomic DNA carries hereditary information, and is the white-print of the most of the living creatures, study of genes, or genomics, has been a subject of intense developments. This excitement was translated in a slogan that «cancer is the disease of genes». The slogan's correctness is questionable today, as the non-genomic mechanisms may have a strong impact on tumorigenesis. How many genes do humans have? What is the structure of these genes, as introns and exons? What type and how many mutations are in the genome of a given patient? What are epigenetic changes in the genes? All these questions have importance for understanding of carcinogenesis, and subsequently for treatment of cancer. In this section are discussed technologies for studies of genome, which may have a valuefor clinical

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applications (Fig. 2). These technologies have been developed to the extent that they may be applied in the clinic for diagnostic, selection of treatment and monitoring of response of a patient.

Massive parallel sequencing (MPS/NGS) The excellent research on biochemistry of DNA paved the way to development of DNA sequencing techniques. The first generation DNA sequencing methods are Maxam-Gilbert fragmentation and Sanger's dideoxy base-termination techniques [13, 14]. However, these techniques in their original forms were too cumbersome for being used in the clinical practice. The step toward clinic was by introduction of automated sequencers [15]. Automation allowed to detect gene mutations of the clinical importance. However, it was still far from a comprehensive analysis of the whole genome of a patient in the routine clinical practice. Faster and affordable methods were needed, and they come with development of massive parallel sequencing (MPS), known also as the next generation sequencing (NGS). MPS is based on parallel sequencing of short fragments of DNA, which are then aligned to produce gene sequences (Fig. 2, A). The size of sequenced fragments is from 30 to 700 bases, depending on the sequencing method and instrumentation [6, 7]. This re - latively short length of the sequenced fragments imposes limitations on the quality of definition of the complete genes sequence. MPS has been used successfully for analysis of mutations in genes, with the emphasis on the exon analysis. Focus on exons allows generation of data which could be used in clini - cal diagnostics within relatively short assay time. As an example, the full exon sequencing and detection of the mutation profile of a tumor cells may be completed within 30 days [8, 9]. The second example is the contribution of MPS to profiling of mutations in different sub-types of cancer, providing insights into molecular heterogeneity of tumors [9]. Understanding this heterogeneity is essential for development of personalized treatment of patients. The expectation is that MPS will become a standard and routine examination of cancer patients. The nearest years will show whether this expectation will indeed be rea - lized in better treatment of patients. CGH, PCR, FISH and ChIP tests Pre-MPS era had given rise to a number of methods to assess structure and mutations of the genes (Fig. 2, B).

Comparative Genomic Hybridization Array (CGH) was used to detect gene aberrations on the whole genome level [10]. However, the resolution power of CGH arrays has been in the range of 5 kB to 0.2 kB, and variations in the gene structure have been the core information delivered by CGH [10]. Fluorescence in situ hybridization (FISH) is used to detect rearrangements of selected genes, e.g. deletions, amplifications and translocations [1, 2]. Clinical application of FISH is limited by its low number of monitored DNA fragments, and relatively large work-load for performing the test. Multi - plexing FISH by using different probes with different detection wavelength, and use of nano-devices to minimize and automate the test are 2 developments which make FISH still useful in the clinical diagnostic [1, 2]. Polymerase-chain reaction (PCR)-based analysis of the genomic DNA is used less and less in the clinical diagnostic. The niche for PCR has become analysis of pre-selected mutations [3]. However, PCR is more used for analysis of RNAs than genomic DNA. Chromatin Immuno-Precipitation (ChIP) has proven the high informative value in studies of chromatin re-arrangements and methylation of the genomic DNA [4]. Therefore, the unique information which may be delivered by ChIP tests is the profile of epigenetic changes in the genome. On the other hand, complexity of the ChIP tests limits its clinical applications.

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Complexity and low automation level of the CGH array, FISH, PCR, and ChIP tests are major hinders for their use in routine clinical diagnostic (Fig. 2, B). Cost efficiency of these assays is also lower, as compared to tests with the recent developments of MPS. Therefore, each of the genome profiling technologies will have their niches. MPS will with high probability dominate the whole genome profiling, while CGH, FISH, PCR and ChIP tests will focus on selected genes and genome areas.

Transcriptomics Historically, mRNA profiling by expression arrays has been the first true OMICs technology. The ground of this technology was laid by excellent works on the biochemistry of oligonucleotides and generation of cDNA. PCR-based analysis of mRNA expression was competing with the RNA expression arrays, but PCR was inferior due to the higher complexity and lower robustness. mRNA profiling has also been proposed for the clinical diagnostic. However, arrival of the massive parallel sequencing technologies has given the real boost to RNA profiling by providing flexibility, speed and additional information about mRNA, microRNAs and long non-coding RNA, e.g. expression and mutations [2]. Massive Parallel Sequencing of RNAs MPS technologies used for profiling of RNAs are similar to those used for profiling genomic DNA, but the focus is on mRNA, siRNA/miRs, and lncRNA. The difference is only in preparation of samples for analysis [6–9]. RNAs are more sensitive to degradation, located in nuclei and cytoplasm, and have different sizes, as compared to the genomic DNA. These features make challenging MPS of RNAs, as variability in quality of the samples would be reflected in discrepancies of produced data. Despite the challenges, information delivered by MPS of RNAs allows better insight into molecular activities in the tumors. A number of examples confirmed value of RNA MPS for making clinical decisions [10, 11]. For example, MPS sequencing of RNAs in tamoxifen-resistant breast cancer cells identified 1728 RNAs associated with the resistance. This number of the affected RNAs indicates that the acquisition of the tamoxifen resistance is a complex process, with involvement of many activities. On the other side, this study opens for better monitoring of the resistance, and the most important, it provides the basis for selection of more efficient treatment by combined blocking of the key RNA-related regulators of the resistance [1].

Expression arrays RNA expression arrays are undergoing evaluation of their use in the clinical diagnostic. Only 5 years ago, RNA expression arrays were at the leading edge of entering clinical diagnostic. The limitation at that time was not in the technology itself, but in applicability of the generated information for diagnostic and making decision about treatment. While measuring expression of RNA provided large volumes of information for research purpose, this information was difficult to translate into diagnostic and prognostic values. The reasons were discrepancies between mRNA expression and expression and activity of the correspon - ding proteins. Another critical limitation was not sufficient robustness of the arrays. As an example, RNA microarrays from different suppliers could produce different detection values for the same RNAs [2]. The niche for RNA expression arrays is changing from the all-gene coverage approach to measuring a set of RNAs of importance for specific type of cancer or a set of cancer drugs. Such arrays are combined now with dedicated systems biology tools to extract disease-relevant information. For example, the arrays have been used to identify long non-coding RNAs associated with breast cancer [3]. MicroRNA arrays are another novel nicheapproach that may be the way to discover cancer-associated microRNAs [4]. PCR-based analysis PCR-based RNA analysis is in the

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situation similar to RNA expression arrays. Notably, PCR-bases analysis is not anymore considered for a comprehensive full-transcriptome screening of RNA expression. PCRbased analysis is currently used for measuring defined sets of up to 100 different RNAs, predominantly mRNAs. For example, focused analysis of expression of the key genes involved in acute myeloid leukemia unveiled 19 up-regulated and 25 down-regulated genes [5]. An important advantage of the PCRbased assays is their technical simplicity. Such assays may be used even in a small size laboratory, and for the low cost. Introduction of companion diagnostic into clinical practice also contributes to the niche-development of PCR-based tests. As examples, PCR-based tests of mutations in BRAF, EGFR, BCRABL, PDGFRs and MEK1 genes are proposed to the clinic as companion diagnostic of drugs acting on these kinases [6, 7]. Thus, MPS technologies have begun to dominate a comprehensive RNAs profiling, while RNA expression arrays and PCR-bases assays are specializing in measurements of pre-selected sets of RNAs. It has to be notes that the recent developments of systemic analysis tools have strongly contributed to extraction of information useful for clinical diagnostic, prognostic and selection of treat ment.

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