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EDITORIAL

Modern Biochemistry in Research of Human Malignant Cells and Experimental Oncology

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ABSTRACT

Modern biochemistry or biochemistry of 21th century is developing in many traditional fields: investigations of proteins, nucleic acids, lipids, carbohydrates, metabolites and metabolic processes, etc, however it has gained new features that based on success of Human Genome Project and on application of high performance technologies (post-genomic technologies). As a result, at the turn of the 21st century some new scientific disciplines, named "OMICS" (proteomics, transcriptomics, lipidomics, glycomics, metabolomics, etc) were created through advances in the biochemistry. Currently "OMICS" and post-genomic technologies are involved in mainstream of cancer research, including studies of human malignant cells. Since malignant tumors consist of heterogeneous cancer cells, the cultured cell lines have some advantages over biopsy simples for studies aimed at understanding the molecular basis of carcinogenesis. The malignant human cell lines differ considerably in their origin from tissues or organs, and therefore they vary widely in the differentiation characteristics and the gene expression patterns. Thus, the use of malignant cell lines ex vivo (as models of human cancers) is an important trend in search for key molecules of carcinogenesis in experimental oncology.

Key words: "OMICS"; Systematic analysis; Human malignant cells; 2D and 3D cell culture models

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EDITORIAL

The biochemistry has a place of honor among the life sciences largely due to its fantastic success in 20th century. Traditional biochemistry started with the study of chemical components of living organisms and their metabolism that provides life itself, and with description of the main types of biopolymers and other biomolecules. At that time technologies allowing to determine sequence of monomers in complex polymers such as nucleic acids and proteins (sequencing technologies) were designed. As a result, in the 80s of the 20th century the entire human mitochondrial genome was identified, heavy and light mitochondrial DNA strands maps were constructed and their nucleotide sequences were determined[1,2].

Further similar studies were concerned with the complete genome sequencing of different bacteria and some eukaryotes[3-5]. In the last decade of 20th century the DNA sequencing of the human nuclear genome was started that influenced the development of the life sciences[6-8].

To achieve the goal of determining the DNA sequence of the entire human genome the considerable resources of the international

community were mobilized and major research projects such as Human Genome Project were realized. After publication of results of human genome identification[9-11], corresponding data were added to publicly available databases (for example, NCBI).

At the turn of the 21st century new stage in development of the life sciences was started known as "post-genomic era", wherein many medical and biological problems including malignant tumors have been studied[12-16].

One of the distinguishing features of post-genomic era in the development of the life sciences is the emergence of new scientific disciplines (or research directions), that have names ending in "-omics". The declared goals of "OMICS" disciplines are the specialized studies of different chemical compounds of living organisms. Thereby relationship between biochemistry of 21st century or modern biochemistry and various "OMICS" disciplines deserves special attention.

Modern biochemistry and "OMICS"

In a second half of the 20th century traditional biochemistry was already represented as multidisciplinary science in which various scientific disciplines are being formed and successfully developed. In particular, protein biochemistry, biochemistry of nucleic acids, biochemistry of lipids, carbohydrate biochemistry, biochemistry of metabolites and metabolic processes are considered as separated disciplines.

Traditional biochemistry usually used the research approach based on extraction of one component from biomaterial with further characterization and «step by step» detection of other related compounds. Currently this approach is still used adjusted for higher technological level, however other approach based on parallel study of large amount of molecules in certain organisms was introduced in the last two decades of 20th century. This approach called "systematic analysis" could theoretically allow to receive comprehensive molecular data for species of interest, particularly *Homo sapience*[17-20]. Apparently, the first manifesto of this approach was published by Anderson N.G. and Anderson L. (1982)[17], who proposed to create the complete catalog of human proteins based on application of two-dimensional electrophoresis.

In the late 1980s, the systematic analysis was already strongly associated with genome-wide studies considered as the basis of a new science known as "genomics". The introduction of the term "genomics" is generally attributed to T. Roderick (by Primrose, Twyman[21]). However, the earliest mention of this term in Pubmed database belongs to Ferguson-Smith, Ruddle (1988)[22] and Willard (1989)[23].

Genomics was a first "OMICS" science, which had special objects of research (genomes of various organisms) and specific tasks (determination of complete nucleotide sequences of studied genomes and mapping of all identified genes) that were solving by using of sets of special methods and techniques[21].

To the beginning of 21th century the genomes of several hundred viruses, natural plasmids, mitochondria and other organelles, 31 types of microorganisms, 7 species of archaea, etc were decoded[24,9,25]. It is especially important that five eukaryotes including *Saccharomyces cerevisiae*, *Arabidopsis thaliana, Caenorhabditis elegans, Mus musculus* and even *Homo sapience* have been among the organisms with sequenced genomes.

Soon after the genomics started, the generalization of results of systematic analysis to protein research led to formation of new discipline that was named "proteomics" by analogy with genomics[26,27].

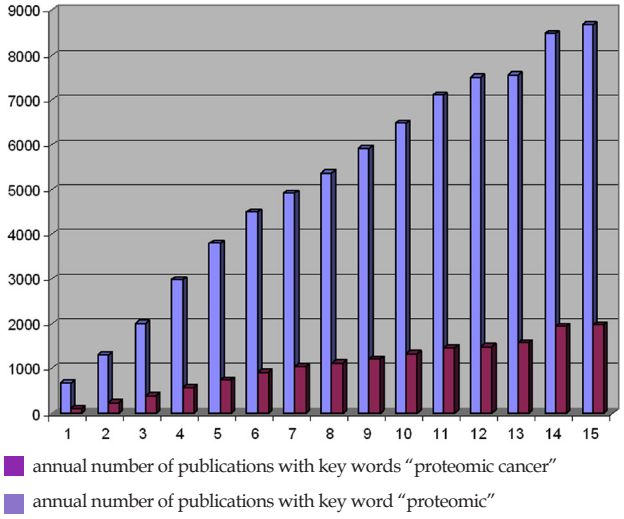

Figure 1 Dynamics of the growth in number of proteomic publications registered in the PubMed NCBI database during 2001–2015 (columns 1–15, respectively).

The term "proteome" («PROTEOME: entire PROTEin complement expressed by the genOME») was first defined and introduced in science on the 1994 Siena conference "2D Electrophoresis: from protein maps to genomes"[26,28]. The author of the current article attended this historic meeting and made a report «Two-dimensional electrophoresis and microsequence analysis of proteins in Russian human genome project».

The methodical arsenal of modern proteomics offers a variety of technologies and methods described in numerous publications on those topics. The number of proteomic publications in PubMed NCBI database was gradually increased in the post-genomic era (2001-2015) to the level of more than 8,000 publications per year (Figure 1). It also should be noted that number of proteomic publications dedicated to cancer research nearly reached 2,000 per year in 2014 and 2015.

The concept of «transcriptome» and «transcriptomics» entered the scientific literature soon after the "proteome" and "proteomics" terms. The term "transcriptome" was coined by Velculescu *et al* (1997)[29] to describe the whole set of RNA (transcripts) produced from expressed genes that can be studied using serial analysis of the gene expression. The word "transcriptomics" apparently appeared for the first time in the journal Nature in 1999 [Nature. 1999 Dec 16; 402(6763): 715]. Two years later the group of French scientists used this term for research of expression profiles (transcripts) at breast cancer[30].

The popularity of genomics, proteomics and transciptomics in 21th century contributed to the development of novel fields of research containing the ending "-omics" which represents the organic relation between genome studies and these disciplines. The neologism "OMICS" is frequently used as a common name for such scientific areas as metabolomics, glycomics, lipidomics and others (alongside with listed above genomics, proteomics and transciptomics). The objectives of metabolomics, glycomics and lipidomics are biomolecules that only indirectly linked with the functioning of genome in contrast to proteomics or transcriptomics. Nevertheless the systematic analysis and mass spectrometry technologies are methodological basis of all of these "OMICS" disciplines[31-33].

It should be noted that the great information banks (in particular of human biomolecules) play a significant role in the development

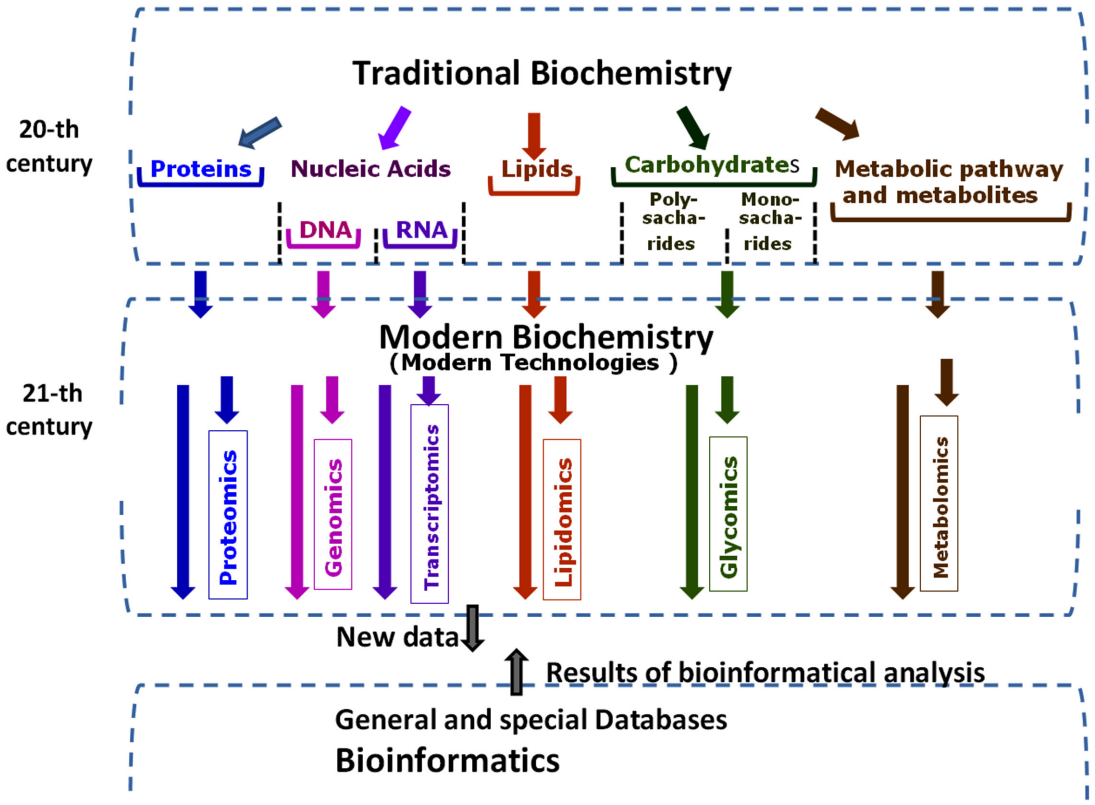

Figure 2 The scheme of interconnection between multidisciplinary traditional biochemistry, modern biochemistry and "OMICS" disciplines with bioinformatics.

of "OMICS" and of modern biochemistry as a whole. These massive amounts of information are summarized in general or specialized databases that require appropriate software for effective using of containing data. Thereby bioinformatics is considered a relatively new science and an essential part of modern biochemistry.

The scheme of interconnection amongst multidisciplinary traditional biochemistry, modern biochemistry and "OMICS" disciplines with bioinformatics is shown in figure 2.

As shown in figure 2, the bioinformatics allows to summarize the data obtained using different "OMICS" technologies. It is affected on progress of systematic analysis to multi-omics approach which is currently used for various kinds of research including study of human malignant cells[34,35].

Modern biochemistry and post-genomic technologies in research of human malignant cells

At the beginning of the 21st century, cancer remains one of leading causes of morbidity and mortality worldwide[36,37]. Respectively, the study of human malignant tumours is important field for application of post-genomic technologies in modern biochemistry. The results of these studies are expected to resolve a number of fundamental and applied problems, including the creation of new efficient methods for diagnostic and target therapy.

In general, malignant tumors have some properties (uncontrolled cell growth, invasiveness, metastatic capacity, and others), related to altered gene expression. Sometimes cancer is even described as a disease of the altered gene expression[38].

Proceeding from the ideas on the mechanism of cancer development, it is supposed that identification of biomolecules that provide the listed properties of malignant cells will allow to find effective diagnostic markers and potential therapeutic targets in cancer. Suitable biomolecules have been looked for a long time in «cancer – noncancer» comparative studies. However a number of difficulties in such studies have been known since traditional biochemistry era.

For example, it has been established that human malignant tumors have various origin, and, therefore, tumor cells significantly differ on types of differentiation and, respectively, on sets of expressed genes.

The most of human malignant tumours fall into one of subsequent main groups according to their origin:

(1) Cancers (carcinomas) – malignant neoplasms of epithelial origin. The most of them are adenocarcinomas, there are also cancers consisting of the partly differentiated cells (follicular carcinoma, squamous cell carcinoma, etc.) and of poorly differentiated cells (small-cell carcinoma, mucinous carcinoma, etc.).

(2) Leukemias and tumors of the hematopoietic and lymphoid tissues, for example, lymphomas. Leukemia (leukosis) – malignant neoplasma of the blood cells in the bone marrow; leukemias are subdivided into two forms – acute and chronic. Lymphomas (lymphosarcoma) – subgroup of blood cell tumors that develop from lymphatic cells of lymph nodes or other lymphoid tissues.

(3) Osteo- and chondrosarcomas – malignant tumors from transformed cells of mesenchymal origin including poorly differentiated cells. Osteosarcoma – malignant neoplasm that arises from primitive mesenchymal cells. Chondrosarcoma – malignant tumor derived from transformed mesenchymal cells that produce cartilage.

(4) Rhabdomyosarcomas and leiomyosarcomas – malignant tumors from skeletal (striated) muscle cells and smooth muscle cells, respectively.

(5) Glioblastomas, neuroblastomas and other malignant tumors

of the nervous system that start from the transformed very primitive nerve cells that seem to be very similar to cells found in an embryo or fetus[39].

Besides, tumors have turned out to be composed of cells with heterogenic morphology and differ on many functional properties, in particular on metastatic potential. It is obvious that such heterogeneity needs to be considered at biochemical research of biopsy samples. The problem of intratumoral morphological heterogeneity has been studied in a second half of the 20th century[40,41], and is still actual in the post-genomic era. It is enough to note that several dozen articles about cellular diversity in malignant tumors were published in first half of 2016[37,42-45]. In particular, Gay *et al* (2016)[42] analyzed and summarized in their review more than 30 publications concerning cellular heterogeneity of various malignant tumors (kidney, lung, colon, mammary gland, prostate, ovary, etc.). The genetic, epigenetic, and phenotypic mechanisms of intra-tumor cell heterogeneity have been described[42,46,47].

Traditionally tumor cell heterogeneity was explained with a clonal selection and adaptation models. These models propose that genomic instability within the primary tumor results in cell diversity due to mutations in subset of tumor cells (e.g. review Ahmed, Li 2013[48]). In additional, the cancer stem cell theory has been proposed[38,49,50]. Cancer stem cells (CSCs) are a subpopulation of tumor cells that have the capacity to self-renew, provide life-long cell growth and produce distinct cell clones[49-51]. The detailed analysis of properties and methods of isolation of CSCs has been presented in a series of reviews. For example, Moghbeli *et al* (2014)[52] introduced different protocols used to isolate CSCs from solid tumors of colon, esophagus, liver, breast, brain, and cervix. The isolation of CSCs can be accomplished by selection of tumor cell subpopulations based on expression of one or more of cell surface markers associated with cancer self-renewal such as: CD133, CD166, CD44, CD24, beta1 integrin-CD29 and others[47,53].

The alternative hypothesis suggested that tumor growth could be mediated, at least in part, by the coalescence of multiple tumorigenic foci within a tissue, a process that would contribute to tumor heterogeneity[40,46,54-56]. In particular, mediated coalescence as a possible mechanism for tumor cellular heterogeneity was recently supported by experimental data obtained from 3D matrigel model[46].

One of the significant aspects of the tumor cell heterogeneity associates with the circulated tumor cells (CTCs). CTCs are subpopulation of cancer cells that has been found in patients with cancer and reported since 19th century (according to Andree *et al* 2016[57]). CTCs are known to be highly heterogeneous, and among them CSCs were detected[58,59]. A large number of studies have been devoted to characteristics and methods of separation of CTCs[60,61]. Collection of blood of cancer patients for isolation and analysis of CTCs is sometimes referred to "liquid tumor biopsy"[61].

As an alternative to traditional heterogeneous biopsy samples, the cultured cell lines derived from various malignant tumors have been actively used since the middle of the 20th century[62,63]. Herewith, the biochemical methods were often used to characterize cultured cell lines, for example, to determine the isoenzyme profiles[64].

In 21st century many cancer cell lines are considered to be important materials for post-genomic research in modern biochemistry[35,65]. Cultured cells are maintained in special biorepositories, for example, American Type Culture Collection, ATCC, or Multidisciplinary Biospecimen Bank[66].

The importance of malignant cell lines as materials for wide range of research has been underscored by the creating of a special database, called Cancer Cell Line Encyclopedia[67]. This large database (CCLE, http://www.broadinstitute.org/ccle/home) contains the gene expression data and some other molecular-biological and biochemical characteristics of 947 human cancer cell lines derived from 36 types of malignant tumors with different level of differentiation. In addition, this database includes the information on the effect of 24 chemotherapeutic agents on 479 cancer cell lines. Thus, according to the creators, CCLE can be useful for predictive modelling of anticancer drug sensitivity. For example, Sonkin *et al* (2013)[68] used CCLE and systematic analysis for study of functional status of 69 tumor suppressors in 799 cell lines annotated in CCLE.

A necessary condition for the experiments in molecular oncology, including the identification of key molecules in the pathways that lead to carcinogenesis, is the standardization of cancer cell lines[69,70].

Evidently, there is a considerable potential for malignant cell lines in experimental oncology.

Human malignant cells and post-genomic technologies in experimental oncology

Modern experimental oncology uses many different models for solving in the preclinical phase important problems associated with the emergence and growth of malignant tumors, as well as with the screening and evaluation of potential anticancer drugs.

Human and animal malignant cell lines are used as model systems in various experiments both ex vivo and in vivo[71-74]. Along with the cancer cell lines, that relate to continuous cell lines and can be obtained from various cell repositories, the primary cell cultures continue to be used as experimental models for cancers[75,76]. Some main models used in experimental oncology are shown in figure 3.

One of the major goals of experimental oncology is the study of key molecules that involved in carcinogenesis. It is believed that such molecules could be potential biomarkers and/or targets for chemotherapy. The use of malignant cell lines and technologies of modern biochemistry is an effective basis for searching for key molecules ex vivo[77-82].

Ex vivo culture systems in experimental oncology are also used for study of potential anticancer drugs. Several recent reviews have been dedicated to this problem, e.g. Lengyel *et al* (2014)[72]; Niu, Wang (2015)[73]; Gazdar *et al* (2016)[74]. The above mentioned Cancer Cell Line Encyclopedia was created as a tool that may help to enable preclinical stratification schemata for anticancer agents[56].

However, the use of ex vivo culture systems is associated with some limitations, for example, see Gazdar *et al* (2016)[74]. In

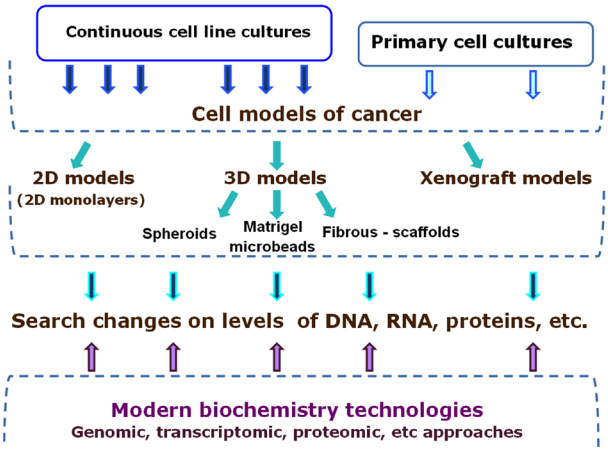

Figure 3 Some main cellular models used in experimental oncology and relationship with technologies of modern biochemistry.

particular, during repeated passaging of cell lines the oligoclonal selection and substantial genetic differences from the original cells can occur. Besides, cell lines are often grown in a 2D monolayer format with no tumor stroma and blood vessels, and it should be considered in interpretation of the obtained results.

To reduce the role of these limitations, 3D cell culture models were created that more accurately represent the in vivo cells composing malignant tumors[83,84]. Beginning at first publications[85,86] and over the past decade, several types of 3D-cell models have been developed. 3D-cell systems as model tumors can include cells cultured as multicellular aggregates (spheroids) and the cells embedded in constructs made of natural or synthetic matrices[84]. Only in 2015 more than 449 scientific articles on 3D-cell models of cancer were published and annotated in NCBI PubMed.

Ex vivo model systems based on malignant cell lines not allow to estimate the effects of anticancer drugs on other cells and organs of human body. However, the results of such side effects can be critical. As a consequence, extrapolation of data obtained from ex vivo cell models requires great caution.

More adequate results can be obtained from various xenograft tumor models using malignant human cells transplantation into animal hosts[87,88,84].

Bibliometric analysis of publications in PubMed NCBI indicates the intensification of studies using xenograft tumor models. The total number of publications on this topic is around 25,000, and more than half of them (14459) have been published in the last 5 years. In many of these works the "OMICS" technologies or even multi-omics approach were used to study of tumor xenograft models[35].

In general, studies of human malignant cells using post-genomic technologies can currently be considered one of the most important and actively developing areas in experimental oncology.

"OMICS" technologies in clinical biochemistry of oncological diseases

In the second decade of the 21st century, "OMICS" technologies are actively used in clinical biochemistry and especially in clinical biochemistry of oncological diseases. General information about scientific publications in PubMed NCBI database related to these fields is shown in table 1.

As can be seen from the table, hundreds or even thousands of papers are published each year, dedicated to application of four main "OMICS" technologies in clinical biochemistry and in clinical biochemistry of cancer.

Most of these studies have been concerned with the various known or potential biomarkers which, according to the authors, could be useful for the following clinical goals: (1) establishment and/or verification of diagnosis, including the origin of malignant tumors; (2) identification of disease stage, including the detection of metastases; (3) prediction of survival based on the origin of malignant tumor; (4) evaluation of treatment effectiveness, including the drug-resistance in cancer cells, and monitoring of remission; (5) detection of cancer recurrence.

The vast majority of such biomarker studies used the samples of blood serum, urine, cerebrospinal and other biological fluids as biomaterials. The cellular and molecular biomarkers, including circulating human tumor cells, exosomes, macromolecules (especially proteins, DNA or RNA) and various metabolites, were analyzed.

As noted above, the methods of detection of circulating tumor cells in patients with malignant tumors are being actively developed in the 21st century[57-59], and the "OMICS" technologies are

Table 1 Publication activity (2011-2015) reflecting the application of four main "OMICS" technologies in clinical biochemistry and in clinical biochemistry of cancer.

Fields (keywords that were used to search in PubMed)	Years				
	2011	2012	2013	2014	2015
Clinical genomic	8 449	9 251	10 516	13 471	14 285
Clinical genomic cancer	661	3 303	3 792	5 194	5 562
Clinical transcriptomic	104	115	135	207	298
Clinical transcriptomic cancer	51	42	53	85	132
Clinical proteomic	1 016	1 110	1 163	1 508	1 716
Clinical proteomic cancer	411	394	446	508	630
Clinical metabolomic	244	308	375	578	712
Clinical metabolomic cancer	70	67	79	166	191

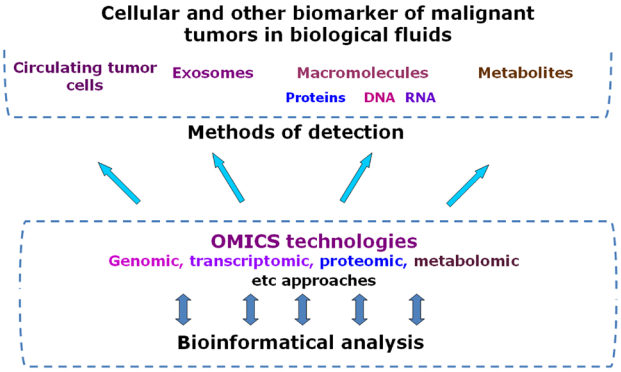

Figure 4 The scheme of the application of "OMICS" technologies for detection of cellular and other biomarkers in biological fluids of patients with malignant tumors.

widely used for solving this problem[89,90]. In particular, currently, considerable attention is paid to so-called exosomes produced by malignant cells. Exosomes are small vesicles with a diameter of 30 to 100 nm that are secreted into the bloodstream and urine, have some specific molecular biomarkers and can be used for diagnostic purposes[91-94]. So, Redzic *et al* (2014)[91] described exosomes from malignant cells of glioblastoma multiforme as stable, membrane-enclosed particles released from the cell surface and accessible in biofluids, such as serum/plasma, urine, cerebrospinal fluid, and saliva. Proteomic analysis and other modern biochemistry technologies revealed that exosomes carry a wide variety of proteins, nucleic acids, lipids, and different metabolites allowing to identify the cell of origin of the vesicles. Accordingly, many authors consider exosomes the potential carriers of cancer diagnostic biomarkers[91-94].

For detection of molecular biomarkers in biological fluids by "OMICS" technologies a very traditional approach is typically used, but on the modern methodical level. This approach consists in comparison of biomarker value in the group of patients with cancer and in healthy control. For example, two samples of urine are separately analyzed by LC-MS/MS[95]. The proteins are identified from fragmented ion spectra. The relative quantification of a protein is obtained from the relative quantification of the corresponding peptides. Each appropriate peptide is quantified by integrating the area under the pseudochromatograms constructed of the precursor ion peak heights generated from the first stage mass analysis of precursor ions (MS1). The essential element in constructing the pseudochromatograms is to obtain peak heights of identical precursor ion masses, expected to represent identical peptides, along the corresponding LC elution period.

The scheme of the application of "OMICS" technologies for detection of cellular and other biomarkers of malignant tumors is shown in figure 4.

Thus, the "OMICS" technologies formed during realization of

the fundamental research projects such as the Human Genome Project came to practical application for decision of different clinical problems in oncology. Accordingly, it is possible to think that in the near future the significant progress will be made in this area.

CONCLUSION

Since the beginning of the 21st century, the application of systematic analysis to biochemical research has been widely developed due to highly efficient technologies. Besides, the general or specialized databases and methods of bioinformatics are using actively. In fact, biochemical studies made a step change that can be evaluated as a transition from traditional to modern biochemistry. The evidence of this transition is the forming of whole set of new scientific "OMICS" disciplines giving new possibilities for medico-biological studies including studies of malignant tumors. Accordingly, the application of technologies of modern biochemistry (including omics-technologies) for the study of cultured malignant cells can be considered as a promising front in cancer research and experimental oncology.

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