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MODERN APPROACHES IN PERSONALIZED MEDICINE. NEW STAGE OF DEVELOPMENT OF IMMUNOGENETICS

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Abstract. The priority direction of modern medicine became a personalized approach to the treatment of patients. It became possible on the background of the active development of genetics. Studies of single nucleotide polymorphisms show a high degree of association with the occurrence, course and prognosis of many diseases. Moreover, these studies in this area show that even minimal differences in the genome may be accompanied by different response to therapy.

Modern methods of DNA studies allow us to determine with a high degree of reliability point changes in the nucleotide sequence. Moreover, the results of scientific research are already being used in medical practice.

Genomic Laboratories revealing genetic risk factors for certain diseases have been used currently in medical practice that contributes to their early diagnosis. In addition, the selection of individual drug therapy based on differences in individuals' genes is also being carried out. This allows to individualize the therapy, which promotes more effective treatment of these diseases.

Development of technology for the production of monoclonal antibodies allows to obtain specific antibodies to membrane and soluble protein structures involved in the pathogenesis of various diseases. Thus, it becomes possible to treat cancer, autoimmune, allergic, and some other diseases.

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СОВРЕМЕННЫЕ ПОДХОДЫ ПЕРСОНАЛИЗИРОВАННОЙ МЕДИЦИНЫ. НОВЫЙ ЭТАП РАЗВИТИЯ ИММУНОГЕНЕТИКИ

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Ключевые слова: иммуногенетика, персонифицированная терапия, моноклональные антитела, полиморфизм генов

Аннотация. В данном обзоре представлена информация о направлениях развития персонализированной медицины, основные аспекты диагностики, лечения и профилактики, основанные на достижениях современной генетики. Основное внимание уделено персонифицированной терапии на основе моноклональных антител, что является новейшим направлением в лечении онкологических, аутоиммунных и ряда других заболеваний.

President's message reads, "Kazakhstan - 2050" as one of the key priorities of the nation's health indicated that the development of preventive medicine should be the main instrument for the prevention of diseases. The solution to this problem may be the advances in medical genetics. Decoding the human genome has created real preconditions for the development of personalized medicine.

In 90s of 20th century American scientist Leo Holland suggested the model of patient-oriented diagnostics and treatment, where creation of multifactorial details suppose registration of biological and psychosocial peculiarities of each patient.

The term “personalized medicine” appeared in 1998, in monograph of Keval Jane. New direction is connected with molecular medicine and ensured the development of relevant innovative technologies. According to research by the Boston Consulting Group (BCG) growth rate of personalized medicine by 2020 will amount to 37% annually (1).

Modern personified medicine develops in three classical directions. They are: diagnostics of pathological condition as in clinical so in the first place on pre-clinical stages, its treatment and prevention of pathological conditions.

We consider the development of each of the areas at the present stage.

Personified diagnosis.

This direction is more important in conception of personified medicine. It is realized through searches of biological connections (biomarkers) that show some specific disorder or exposure. By using biomarker molecules processes of cell damage, DNA, RNA, protein precursors which are detected by methods based on nanobiotechnology can be determined (2). In this case, the nanomaterials are used to create biomarkers (3). Examples of such biomarkers may be the so-called quantum dots that are used for identification of early stages of carcinogenesis process (4), and micro-metastases (5), as well as other diseases (6). The use of nanobiotechnology to proteomics, nano proteomic analysis contributes to the creation of modern proteomic database and allows to identify trace amounts of proteins in extremely small volumes of test samples. In the future, nanobiotechnology will allow creating nanoscale devices for rapid screening of biomarkers that identify the stages of development of rarely detected human diseases (2). Thus, nanobiotechnology overcome the limitations of modern methods of molecular diagnostics, contribute to the establishment of a fast, accurate and comprehensive diagnosis and contribute to the integration of diagnostic programs of research with therapeutic activities of the personalized approach to the patient (7).

It is expected that with development of analytical methods practice doctor can understand information about markers in the level of genome, transcriptome, proteome and metabolome.

Regarding personalized genomic characteristics, they allow to determine the nature and origin of the disease or response to certain treatments. For today there is evidence that the presence of even small individual differences in DNA in two patients they can respond to the same drug differently (8).

Human genome researches attract scientists from many countries. For example, for decoding of the genome in 1990, the United States government approved the project "Human Genome". The cost of sequencing the genome of a primate at that time was about $ 20 million. To reduce the cost of human genome sequencing procedure to $ 1000 "Personal genome" project was initiated (9).

In just a few years a number of technical problems have been overcome, and the latest innovative technology genome sequencing allows you to quickly and efficiently obtain genomic information (10). It became possible thanks to the innovative technology of decoding DNA molecules during their translocation through the nanopore, placed on a silicon chip (2). For today one of the available for large-scale genomic analysis systems is the platform (454 Sequencing System), which generate hundreds of thousands of high-quality data on the sequence in a few hours. Furthermore, this platform can be the first next-generation sequencing technology, developed for use in clinical conditions (9).

Today there is lots of information about mutation associated with these or other diseases. The most frequent changes in the structure of genes are a single nucleotide polymorphism (SNP). As a rule, to assess the significance of detected individual single nucleotide polymorphisms in the analyzed genes compared their frequency of occurrence between healthy individuals and groups of patients. Today it is defined more than 2,400 identified SNP, was significantly associated with illness.

Modern stage of development of molecular-genetics technology of research considers the regularity connection of individual genetic markers and level of immune reaction of organism. This connection has wide range of severity and condition the differential impact on the course of disease (11, 12, 13 and 14).

Molecular diagnosis demonstrated the most effectiveness of the hereditary form of cancer.

There are lots of works determining personalized genome characteristics connected with oncology. Several authors point out that the genomic profile of biopsy tumor is unique to each patient and reflects both carcinogenic and additional random mutations (15). Specific cancer mutations described in the genomic atlas of cancer - Cancer Genome Atlas (16). However, it is clear that the majority of cancer genes have not been identified yet, which dictates the need for further research (17, 18, 19, 20).

Active research on genetic markers of cancer processes directs the efforts of scientists to search for molecular biomarkers and the development of appropriate test systems. The bases for determination of tumor markers are immunological methods.

The result of great work to identify genetic markers of susceptibility to several diseases, in particular cancer has been the introduction into clinical practice of the relevant oncology tests (to determine the risk of breast cancer - test MammaPrint, OncotypeDx) (18).

At the same time, the possibility of Immunology and Immunogenetics implemented in the art to further personalized treatment of patients with neoplastic disease using monoclonal antibodies.

For example, the identification of polymorphisms (differences) of key genes determines tactics against certain types of cancer. In particular, the efficacy of some types of cancer depends on KRAS mutations in genes, p53, HER2, etc.

Diagnosis pre-symptoms stages can recognize not only rare form of cancer, but some nervous and mental disorders, is now defined only on the basis of clinical symptoms. All of this will be a prerequisite for the development of effective treatments.

As for Molecular Immunology and Immunogenetics, their ability was realized in the study of autoimmune, allergic diseases and immunodeficiencies.

In historical aspects, the immunogenetic studies began long before the formation of the concept of personalized therapy and were devoted to the study of HLA-system.

Thus, for example, the prospects for improving prognosis of rheumatoid arthritis (RA), directly linked to an early diagnosis and appropriate treatment initiated immediately. It is proved that 40 % contributions to the development of genetic systems have to RA gene complex HLA II- class (HLA-DRB1) (21). It is believed that the various variants of genes HLA-DRB1 (01, 04, 10, and 14) encode the synthesis of the amino acid sequence of DR molecules forming the antigen binding groove. These sequences are called " common epitope » (shared epitope). It is assumed that this epitope with high affinity, antigen binding synovial membranes, which leads to the activation of autoreactive clones of T lymphocytes to the articular tissue self-antigens (22). Next to research the relationship associative and the protective effects of HLA genes with respect to the development of RA in representatives of different nationalities with separate variants of genes and haplotypes. In particular, Russian, marker alleles for PA were HLA-DRB1 * 0401, DQA1 * 0301, DQB1 * 0302, and others, while be protective in the development of PA were DRB1 * 11, * 13, * 15, DQA1 * 0102, * 0103 and the other (23). These polymorphisms can be used to pre - symptomatic and differential diagnosis of PA, as well as to create a risk group among close relatives of patients with RA.

A considerable amount of work devoted to genetic determination of allergic diseases (24, 25, 26 and 27). Identified by molecular genetics and immunological studies pathogenetic candidate genes are divided into several groups: antigenic recognition factor genes and hummoral immune responses, inflammatory mediators genes, genes receptors and mediators of hummoral response factors, transcription factors, genes, metabolic genes, including detoxification xenobiotics (25).

It is known that the development of asthma associated with allelic variants of genes HLA-DR13, HLA-DR6, HLA-DR52, HLA-DR4, HLA-DR7 (28, 29). The prognostic and diagnostic value of genetic research has increased with the advent of the possibilities of determining gene polymorphisms of cytokines and their receptors.

At the present stage of development of immunogenetics emphasis in research shifted to the study of cytokine gene polymorphism involved in the formation of inflammation and toll-like receptors. The study of cytokine network activity begins in the 80's of last century. It is proved that the nature and strength of any of the inflammatory process is determined by the relation and interactive regulation of various cytokines that have pro-and anti-inflammatory effects. Actively developing the field of medical genetics at the present stage accumulates information about the relationship of cytokine gene polymorphisms and clinical features of different diseases.

We present only small part of the results of research in this area. For example, studies show that polymorphisms of cytokines and their receptors in the development of allergic diseases are highly professional value TNFA * α allele is associated with an increased risk of developing the disease. At the same time, a group of workers exposed to hazardous inputs, risk factors for developing asthma have been voted genotype IL -4RA * I * I, as well as a combination of genotypes of IL -4RA * I * I-CD14 * C * T

and IL -4RA * I * I- IL -13 * R * R (29).

When analyzing the communication cytokine gene polymorphism with the speed of progression of multiple sclerosis a significant association for rs11086998 polymorphism CD 40 gene (dominant inheritance model) was found (30). Susceptibility to infertility and its associated endometriosis is associated with AA and GA genotype polymorphism G-308A gene TNFA, G allele and the GG genotype of the polymorphic region of T-330G gene IL2, T allele and TT genotype polymorphism C-590T gene IL4 (31).

Similar studies carried out in almost all diseases in the pathogenesis of which pro-and anti-inflammatory cytokines involve. At the same time, national differences in the mutation of a gene predisposing to a particular disease are detected. For example, the Tatars structure of hereditary predisposition to myocardial infarction includes allelic variants of genes TNFA (-308G / A), IL10 (-627S / A). At the same time, the risk of myocardial infarction increased in carriers of genotype TNFA (-308) * G / * G, and demoted from carriers of genotype TNFA (-308) * G / * A. While, the structure of the Russian hereditary predisposition to myocardial infarction includes allelic variants of genes IL6 (-572G / C), IL12B (-1159A / C) and IL1B (+ 3953C / T). At the same time, the risk of myocardial 'infarction increased in carriers of genotypes IL6 (-572) * C / * C and IL12V (-1159) * A / * A, and lowered in carriers of genotype IL12B (-1159) * A / C *. (32).

At the moment, there are already the possibilities of applying the results of scientific research into practical health care. In particular, genetic laboratories studying gene polymorphisms of pro-inflammatory cytokines in order to identify the risk of infertility are widespread.

Personalized treatment.

According to details of worldwide health organization standard therapy treatment is not effective for 40% of sick people.

Individualized diagnosis of pathological conditions arising involves a personalized selection of medicines. Having identified the genetic characteristics of a patient, the physician selects the most effective and safe drug, its dosage and individual treatment. This approach is applicable in many areas of medicine. It also allows you to reduce the cost of expensive medicines, which in empirical choice may not be appropriate for a given patient.

An example of an individual approach is the treatment of cancer. The relevance of this area due to the high resistance of tumor cells to various chemotherapeutic drugs. One strategy is the use of monoclonal antibodies (33, 34, 35, and 36).

At present there are two types of MAB: simple and conjugated, the therapeutic effect of which is due to an antibody attached substances (radioactive particles, toxins or cytotoxic drugs).

Simple monoclonal antibody different exert their effects on malignant tumor. Some of the antibody binding to the corresponding antigen, is launching a natural ¬ governmental mechanisms of immune response, others are not inter ¬ Art ¬ actually exist in the human immune system. Their effect is realized by binding to antigens that provide cell proliferation or tumor growth. Let us consider some of them.

Rituximab (Rituxan, Mabthera) - chimeric monoclonal antibody having a murine variable region and a human constant region, specifically bound to the CD20 antigen on B lymphocytes and initiate immunological responses that mediate lysis of B-cells.

Alemtuzumab (Mabkempas, Campath) - a humanized monoclonal antibody to the antigen CD52. Used for the treatment of chronic lymphocytic leukemia. Variable Region alemtuzumab connected to CD52 antigen on the surface of lymphocytes and constant region - with Fc-receptors on the surface of cytotoxic cells, which destroy the target, is a cell-mediated antibody-dependent cytotoxicity, and activates the complement system.

The mechanism of action of some MAB is implemented without immune mechanisms.

Trastuzumab (Herceptin) is the first humanized antibody HER2/ neu-receptors belonging to the epidermal growth factor receptors. HER2/neu overexpression in breast cancer tissue is found in 20-30% of patients and is accompanied by a reduction of apoptosis, increased cell proliferation, decreased numbers of estrogen receptors in the tumor decrease the effectiveness of chemotherapy and hormonal therapy.

Bevacizumab (Avastin) presents recombinant humanized monoclonal antibody that selectively bind biologically active vascular endothelial growth factor (VEGF) and it's neutralized, which leads to a

decrease in vascularity and tumor growth inhibition. Its application of 25 different types of cancer including breast cancer, colon cancer, clear cell renal cancer, small cell lung cancer, and melanoma is studied.

Cetuximab (Erbitux) - chimeric MAB blocking activation of epidermal growth factor receptor (EGFR). This is used for treatment of colon cancer (in combination with irinotecan), head and neck.

Conjugated monoclonal antibodies are used for the delivery of cytotoxic agents to tumor cells directly, thereby avoiding damage to healthy tissue, solves the problem associated with some weak antitumor effect due to the inability of antibodies to penetrate deep into the fabric of a solid tumor.

As conjugate radioactive particles cytostaticsimmunotoxins.As examples of such antibodies is ibritumomab, tiuxetan (Zevalin) - MAB against CD20, coupled with yttrium-90. They are used for the treatment of relapsed and refractory forms of follicular lymphomas.

Tositumomab (Beksar) - mouse MAB to the antigen CD20, which is attached to a radioactive isotope iodine-131. This is used for the treatment of relapsed follicular lymphoma.

Immunotoxins are obtained by addition to the MAB bacterial (diphtheria toxin, Pseudomonas aeruginosa exotoxin A) or plant toxins (ricin A or saporin).

Gemtuzumabozogamicin (Mylotarg) is used in the treatment of acute myeloid leukemia in the elderly people. Mylotarg represents human antibodies to CD33, which is present on the majority of leukemic cells in combination with a toxin calicheamicin.

It should be noted that not only MAB used in oncological practice but also in other areas of medicine. For example, anticancer antibodies constitute 50% of the market volume of selling drugs MAB, 37% of the market occupied by antibodies for the correction of autoimmune / inflammatory disorders, 11% - MAB for the treatment of respiratory diseases, and 2% - for cardio-vascular diseases.

The most used MAT in treatment of autoimmune disorders is the following formulations.

Monoclonal antibodies to TNF-infliximab (Remicade), adalimumab (Humira). These drugs have shown high efficacy in RA. However, in clinical practice, about 30-40% of patients "refractory" to therapy with these agents is less than half - can achieve complete or partial remission, and about a third forced to stop treatment because of the ineffectiveness of the secondary or side effects after 2-3 years of therapy. The causes of this inefficiency are still open.

Also interesting drug Tocilizumab which is MAB to IL-6R and two signaling pathways inhibits IL-6 dependent cell activation. Taking into account the fundamental role of IL-6 in the development of chronic inflammation, it is possible to predict tocilizumab great potential in the treatment of a wide variety of other so-called **IL**-6-dependent human diseases (SLE, SSD, systemic vasculitis, some forms of malignancy, osteoporosis, asthma, etc.) and their complications.

From the anti-B cell preparations may be mentioned rituximab - MAB to CD20 antigen of B-cells.

Another area of personalized treatment can be called m vaccine development "with a private address." Such vaccines include "vector vaccines" individual cell vaccines and regulation of the immune response using dendritic cells as well as methods of treatment based on autologous stem cells. Such technology is already widely used for the treatment of cardiovascular diseases, cancer, for the needs of regenerative medicine.

Personalized prophylaxis.

Personalized prophylaxis implies a search for genetically "weak points" of the body that lead to the development of a disease, the nature of its flow, resistance to therapy, and other characteristics. There are also some branches in this direction.

One of the determinations of the genetic differences of the human species from other members of the animal world that is the creation of a genetic map of Homo sapiens. This need is caused by incomplete knowledge of which genes make one person, and human disease.

Also it is necessary to make up the document of “ideal health” for people of different races (nations) and comparing analyses. These issues are dealt with population genetics.

Also, you need to create individual genetic maps with the definition of hereditary predisposition of the individual to the social disease (immune deficiency states, cancer, endocrine, psychiatric pathology, myocardial infarction, stroke, etc.). The priority in this case is the identification of carriers of mutations of monogenic diseases, and dominant disease with late “debut ", such as Alzheimer’s, diabetes, hereditary

forms of breast cancer, etc. Also, it is necessary to identify individual susceptibility to the damaging effects of xenobiotics (alcohol, drugs, ionizing radiation, chemical, biological agents, including viruses).

In this way personalized prevention will provide specific recommendations to prevent this disease. These include: early registration, clinical supervision and the use of appropriate methods of detection.

Native scientists are studying the molecular genetic characteristics of various diseases recently. Promising, little -studied trend in this area is the study of the Kazakhs. Genetic markers will have a practical value for the prognosis of formation, characteristics of the course, opportunities for the development of complications and the choice of the most effective personalized therapies. Department of Immunology KazNMU conducting studies to determine the polymorphism of pathogenic significance of cytokines in patients with rheumatoid arthritis in the Kazakh population. Results of the study will form the approaches to the formation of individual algorithms for managing these patients, as well as more effective pre-symptom prophylaxis.

In conclusion, we would like to emphasize the promise of genetic, including immunogenetic studies for the diagnosis, prevention and treatment of many diseases of social importance. In our country the main obstacles for such research and the further application of the results in clinical practice, along with the still high cost of the necessary studies are insufficient training of specialists, the discrepancy between the latest valuable diagnostic and therapeutic possibilities and the ability of practitioners to apply in practice.

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ЖЕКЕЛЕНГЕН МЕДИЦИНАНЫҢ ЗАМАНУИ ЖОЛДАРЫ. ИММУНДЫ ГЕНЕТИКАНЫҢ ДАМУЫНДАҒЫ ЖАҢА КЕЗЕҢ

Кілтті сөздер: иммунды генетика, жекеленген терапия, моноклонды антиденелер, гендердің полиморфизмі.

Түйін: Берілген шолуда жекеленген медицинаның даму бағыттары және заманyи генетиканың жетістіктеріне негізделген диагностика, емдеу және алдын алу шаралары туралы ақпараттар берілген. Онкологиялық, аутоиммунды және бірқатар басқа аурулардың емінде қолданатын жаңа бағыттардың бірі - моноклонды антидене негізіндегі жекеленген медицинаға аса назар аударылған.

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