

1. *Novikova S.E., Kurbatov L.K., Zavalova M.G., Zgoda V.G., Archakov A.I.*

Omic technologies in diagnostics of lung adenocarcinoma.

To date lung adenocarcinoma (LAC) is the most common type of lung cancer. Numerous studies on LAC biology resulted in identification of crucial mutations in protooncogenes and activating neoplastic transformation pathways. Therapeutic approaches that significantly increase the survival rate of patients with LAC of different etiology have been developed and introduced into clinical practice. However, the main problem in the treatment of LAC is early diagnosis, taking into account both factors and mechanisms responsible in tumor initiation and progression. Identification of a wide biomarker repertoire with high specificity and reliability of detection appears to be a solution to this problem. In this context, proteins with differential expression in normal and pathological condition, suitable for detection in biological fluids are the most promising biomarkers. In this review we have analyzed literature data on studies aimed at search of LAC biomarkers. The major attention has been paid to protein biomarkers as the most promising and convenient subject of clinical diagnosis. The review also summarizes existing knowledge on posttranslational modifications, splice variants, isoforms, as well as model systems and transcriptome changes in LAC.

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2. *Gnatenko D.A., Kopantzev E.P., Sverdlov E.D.*

Fibroblast growth factors and their effects in pancreas organogenesis.

Fibroblast growth factors (FGF) are growth factors that regulate many important biological processes, including proliferation and differentiation of embryonic cells during organogenesis. In this review, we will summarize current information about the involvement of FGFs in the pancreas organogenesis. Pancreas organogenesis is a complex process, which involves constant signaling from mesenchymal tissue. This orchestrates the activation of various regulator genes at specific stages, determining the specification of progenitor cells. Alterations in FGF/FGFR signaling pathway during this process lead to incorrect activation of the master genes, which leads to different pathologies during pancreas development. Understanding the full picture about role of FGF factors in pancreas development will make it possible to more accurately understand their role in other pathologies of this organ, including carcinogenesis.

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3. *Shpakov A.O.*

Pharmacological approaches for correction of thyroid dysfunctions in diabetes mellitus.

Thyroid diseases are closely associated with the development of types 1 and 2 diabetes mellitus (DM), and as a consequence, the development of effective approaches for their treatment is one of the urgent problems of endocrinology. Traditionally, thyroid hormones (TH) are used to correct functions of the thyroid system. However, they are characterized by many side effects, such as their negative effect on the cardiovascular system as well as the ability of TH to enhance insulin resistance and to disturb insulin-producing function of pancreas, exacerbating thereby diabetic pathology. Therefore, the analogues of TH, selective for certain types of TH receptors, that do not have these side effects, are being developed. The peptide and low-molecular weight regulators of thyroid-stimulating hormone receptor, which regulate the activity of the thyroid axis at the stage of TH synthesis and secretion in thyrocytes, are being created. Systemic and intranasal administration of insulin, metformin therapy and drugs with antioxidant activity are effective for the treatment of thyroid pathology in types 1 and 2 DM. In the review, the literature data and the results of own investigations on pharmacological approaches for the treatment and prevention of thyroid diseases in patients with types 1 and 2 DM are summarized and analyzed.

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4. *Lokhov P.G., Lisitsa A.V., Archakov A.I.*

Metabolomic blood test: purpose, implementation and interpretation of data.

The human body is an open system that receives a variety of xenobiotics in the course of dietary route or respiration and in the form of the drugs. As a lump sum scores of toxic and potentially toxic substances are detected in a human body that significantly affect health and human lifespan. There are also thousands of diseases, dozens of which latently occur in the body of each person. Traditional diagnosis is not able to screen all the variety of xenobiotics and potential human diseases. For this purpose metabolomic blood test is available which is of non-targeted (review) nature. The test can reveal all the diversity of low molecular weight substances in blood, including tens of thousands of xenobiotics and markers of different diseases. Detection of xenobiotics in the blood, directional detoxification and subsequent monitoring of the body's chemical purity together with the control of the normality of all biochemical processes in the organism, using metabolomics blood tests is a necessary and presumably a sufficient condition in the implementation of inherent human genotype longevity. This article describes the purpose, implementation and interpretation of metabolomic blood test facilitating the implementation of this method in the Russian Federation, in order to significantly increase the average life expectancy.

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5. *Kryukova E.V., Shelukhina I.V., Kolacheva A.A., Alieva A.Kh., Shadrina M.I., Slominsky P.A., Kasheverov I.E., Utkin Y.N., Ugrumov M.V., Tsetlin V.I.*

Possible involvement of neuronal nicotinic acetylcholine receptors in compensatory brain mechanisms at early stages of Parkinson's disease.

A role of nicotinic acetylcholine receptors (nAChR) in the development of Parkinson's disease (PD) has been investigated using two mouse models corresponding to the presymptomatic stage and the early symptomatic stage of PD. Quantitative determination of nAChR in the striatum and substantia nigra (SN) was performed using the radioactive derivatives of epibatidine, α -conotoxin MII, and α -bungarotoxin as ligands. The number of ligand-binding sites changed differently depending on their location in the brain, the stage of the disease and the receptor subtype. Epibatidine binding decreased in the striatum to 66% and 70% at the presymptomatic and early symptomatic stages, respectively, whereas in SN a 160% increase was registered at the presymptomatic stage. The α -conotoxin MII binding on striatal dopaminergic axonal terminals at the presymptomatic stage decreased by 20% and at the symptomatic stage it demonstrated a further decrease. The increase in α -bungarotoxin binding at the presymptomatic stage and a decrease at the early symptomatic stage was observed in the striatum. In SN, the level of α -bungarotoxin binding decreased at the presymptomatic stage and kept constant at the symptomatic stage. The significant decrease in the expression of Chrna4 and Chrna6 genes encoding α 4 and α 6 nAChR subunits was observed in SN at the early symptomatic stage, while a 13-fold increase in expression of the Chrna7 gene encoding the α 7 nAChR subunit was detected at the presymptomatic stage. The data obtained suggest possible involvement of nAChR in compensatory mechanisms at early PD stages.

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6. Medvedev D.V., Zvyagina V.I., Uryasev O.M., Belskikh E.S., Bulatetskiy S.V., Ryabkov A.N.

Metabolic changes in pulmonary mitochondria of rats with experimental hyperhomocysteinemia.

Hyperhomocysteinemia is a risk factor for many human diseases, including pulmonary pathologies. In this context much interest attracts secondary mitochondrial dysfunction, which is an important link in pathogenesis of diseases associated with hyperhomocysteinemia. The study was conducted using male Wistar rats. It was found that under conditions of severe hyperhomocysteinemia caused by administration of methionine, homocysteine was accumulated in lung mitochondria thus suggesting a direct toxic effect on these organelles. However, we have not observed any significant changes in the activity of mitochondrial enzymes involved in tissue respiration (succinate dehydrogenase) and oxidative phosphorylation (H^+ -ATPase) and of cytoplasmic lactate dehydrogenase. Also there was no accumulation of lactic acid in the cytoplasm. Animals with severe hyperhomocysteinemia had higher levels of lung mitochondrial protein carbonylation, decreased reserve-adaptive capacity, and increased superoxide dismutase activity. These results indicate that severe hyperhomocysteinemia causes development of oxidative stress in lung mitochondria, which is compensated by activation of antioxidant protection. These changes were accompanied by a decrease in the concentration of mitochondrial nitric oxide metabolites. Introduction to animals a nonselective NO-synthase inhibitor L-NAME caused similar enhancement of mitochondrial protein carbonylation. It demonstrates importance of reducing bioavailability of nitric oxide, which is an antioxidant in physiological concentrations, in the development of oxidative stress in lung mitochondria during hyperhomocysteinemia. Key words: hyperhomocysteinemia, nitric oxide, lung, oxidative stress, mitochondria

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7. Todosenko N.M., Khaziakhmatova O.G., Yurova K.A., Malinina I.P., Litvinova L.S.

The influence of methylprednisolone on the ability of CD4⁺CD95⁺HLA-DR⁺ T-cells to produce proinflammatory mediators in cultures of TCR-activated CD3⁺CD45RO⁺ T-lymphocytes from patients with rheumatoid arthritis.

The effect of different concentrations of the glucocorticoid (GC) methylprednisolone (MP) on CD4⁺CD95⁺HLA-DR⁺ T-cells and their ability to produce proinflammatory mediators in cultures of TCR-stimulated CD3⁺CD45RO⁺ T-lymphocytes in the in vitro system was investigated. T cells were obtained from healthy donors and patients with rheumatoid arthritis (RA). Under conditions of TCR-activation, MP increased the number of CD4⁺HLA-DR⁺CD95⁺ cells in CD3⁺CD45RO⁺ cultures obtained from RA patients and did not change their content in the control group. In general, MP decreased production of proinflammatory factors (IFN- γ , IL-2, IL-17, IL-21 and TNF- α) by TCR-activated CD3⁺CD45RO⁺ cells from healthy donors and RA, consistent with the overall immunosuppressive mechanism of GC action. The correlation between CD4⁺CD45RO⁺HLA-DR⁺CD95⁺ T-cell contents and parameters reflecting production of proinflammatory mediators (IL-17, IL-21 and TNF- α) in RA patients indicates maintenance of the pro-inflammatory potential of this T-cell population exposed to GC action. We suggest that relative resistance of CD4⁺CD45RO⁺CD95⁺HLA-DR⁺ T-cells of RA patients to the suppressor effect of GC leads to maintenance and even enhancement in the functional capacities of autoreactive cells in the pathogenesis of RA.

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8. Pogorelova T.N., Gunko V.O., Avrutskaya V.V., Kaushanskaya L.V., Durnitsyna O.A.

Impairments of placental amino acid metabolism in fetal growth restriction.

The content of the amino acids in the placenta during physiological pregnancy and fetal growth restriction (FGR) has been investigated by means of the method of ion-exchange chromatography. It has been found that in FGR the placental amino acid pool is characterized by a decreased content of arginine, proline, alanine, serine, cysteine, methionine, tryptophan, leucine, threonine, tyrosine, phenylalanine, glutamine and an increased content of dicarboxylic amino acids, lysine, histidine and glycine. These changes are accompanied by altered activity of some enzymes of amino acid metabolism, and the degree of these changes correlates with the level of corresponding amino acids.

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9. Gumanova N.G., Klimushina M.V., Gavrilova N.E., Metelskaya V.A.

Combined markers of initial stages of coronary atherosclerosis.

Abnormalities in energy metabolism and endothelial dysfunction contribute to signaling processes associated with atherogenesis. The goal of our study was to develop diagnostic tests based on endothelial functional markers and adiponectin to differentiate early stages of coronary lesions during atherogenesis. The cohort included male and female patients from 25 to 86 years of age. All subjects underwent coronary angiography and severity of coronary lesions was quantified by the Gensini score that assigns points depending on location and extent of the lesions. We have estimated associations between the Gensini score and some known primary and secondary diagnostic parameters and have found that the ratio of serum levels of

adiponectin to endothelin strongly correlates with severity of coronary lesions and can be used for differentiation of male patients lacking coronary atherosclerosis (despite symptoms of ischemic heart disease) from patients that have severe coronary lesions. Predictive power of adiponectin to endothelin ratio did not depend on drug therapy.

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10. Skvortsov V.S., Alekseychuk N.N., Rybina A.V.

Correction of the electrophoretic shift in virtual 2D SDS-PAGE electrophoresis.

Virtual electrophoresis in proteomics can be used to search localization of proteins and their proteoforms (especially those existing in low concentrations), to identify proteoforms found in experiments etc. Although the problem of predicting the isoelectric point is well studied, the need of electrophoretic shift correction is usually ignored. Researchers simply use the brutto molecular weight of the protein. In this study four data sets taken from the literature sources and the SWISS-2DPAGE database have been used to build correction equations for prediction of the electrophoretic shift (123, 72, 118 and 470 points, respectively). Two groups of models were built. The first model was based on the amino acid composition of proteins, the second one, on analysis of parameters calculated by amino acid sequences (theoretical molecular weight, hydrophobicity, charge distribution, ability to form helix structures). The coefficient of determination ranged from 0.35 to 0.75 in each single set, but cross-prediction between samples did not give satisfactory results. At the same time, the direction of correction was predicted correctly in 74% of cases. After combining of the samples and dividing pooled data into 2 representative sets, the coefficient of determination during in the process of learning ranged from 0.44 to 0.51, and R2 of predictions were not less than 0.39. The direction of correction was predicted correctly in 80% of cases. This prediction models have been integrated into the program pIPredict v.2, freely available at <http://www.ibmc.msk.ru/LPCIT/pIPredict>.

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