

1. Pyatnitskiy M.A., Karpov D.S., Moshkovskii S.A.

Searching for essential genes in cancer genomes.

The concept of essential genes, whose loss of functionality leads to cell death, is one of the fundamental concepts of genetics and is important for fundamental and applied research. This field is particularly promising in relation to oncology, since the search for genetic vulnerabilities of cancer cells allows us to identify new potential targets for antitumor therapy. The modern biotechnology capacities allow carrying out large-scale projects for sequencing somatic mutations in tumors, as well as directly interfering the genetic apparatus of cancer cells. They provided accumulation of a considerable body of knowledge about genetic variants and corresponding phenotypic manifestations in tumors. In the near future this knowledge will find application in clinical practice. This review describes the main experimental and computational approaches to the search for essential genes, concentrating on the application of these methods in the field of molecular oncology.

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2. Mikhaylenko D.S., Prosyannikov M.Y., Baranova A., Nemtsova M.V.

Genetic and biochemical features of the monogenic hereditary urolithiasis.

Urolithiasis is a common urological problem. In most cases, this multifactorial pathology develops due to the combination of inherited low-penetrance gene variants and environment factors such as urinary tract infections and unbalanced diet. However, some cases are monogenic. These hereditary forms of urolithiasis manifest in childhood, and are characterized by multiple, bilateral and recurrent kidney stones and progress to chronic renal failure relatively early. Due to widening acceptance of exome and gene panel sequencing, substantially larger percentages of urolithiasis cases are now attributed to hereditary causes, up to 20% among patients of 18 years old or younger. Here we review genetic and biochemical mechanisms of urolithiasis, with an emphasis on its hereditary forms, including fermentopathies (primary hyperoxaluria, adenine phosphoribosyltransferase deficiency, phosphoribosyl-pyrophosphate-synthetase deficiency, xanthinuria, Lesch-Nihan syndrome) and these caused by membrane transport alterations (Dent's disease, familial hypomagnesemia with hypercalciuria and nephrocalcinosis, hypophosphatemic urolithiasis, distal tubular acidosis, cystinuria, Bartter's syndrome). We suggest a comprehensive gene panel for NGS diagnostics of the hereditary urolithiasis. It is expected that accurate and timely diagnosis of hereditary forms of urolithiasis would enable the counselling of the carriers in affected families, and ensure personalized management of the patients with these conditions.

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3. Komleva Yu.K., Lopatina O.L., Gorina Ya.V., Chernykh A.I., Shuvaev A.N., Salmina A.B.

Early changes in hippocampal neurogenesis induced by soluble Ab1-42 oligomers.

Alzheimer's disease is characterized by the loss of neurons, the accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques in the brain. However, there are contradicting data on differences in neurogenesis at the onset of the disease or before the formation of amyloid plaques. As awareness of the importance of the pre-symptom phase in neurodegenerative diseases grows in the context of early diagnosis and pathogenesis, we analyzed the critical periods of adult hippocampal neurogenesis at an early stage under the action of soluble Ab1-42 beta-amyloid. The proliferation, migration and neuronal cells survival were evaluated in mice with an injection of soluble amyloid beta-oligomers. It was found that the injection of Ab1-42 oligomers causes a decrease in cell proliferation in the mouse hippocampus. Despite the preservation of the neuroblast pool in animals after beta-amyloid injection, the process of radial migration is disrupted, and an increase in apoptosis in the neurogenic niche was revealed. Thus, our results demonstrate damage of neurogenesis critical stages: the progenitor cells, neuroblast migration, the integration of immature neurons, and the survival of neurons under application of soluble beta-amyloid oligomers. The obtained data indicate decline in proliferation rate in the subgranular zone, that is accompanied by ectopic differentiation and disturbed migration, producing, apparently, abnormal neurons that have lower survival rates. That could lead to a decrease in mature neurons numbers and the number of cells in the granular layer of the dentate gyrus.

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4. Popova T.A., Muzyko E.A., Kustova M.V., Bychenkova M.A., Perfilova V.N., Prokofiev I.I., Samoylova M.A., Tyurenkov I.N., Latypova G.M., Kataev V.A.

Influence of the dense extract from herb of *Primula veris* L. On the oxidative stress development and the functional state of the cardiomyocytes mitochondria of rats with experimental chronic heart failure.

Experimental chronic heart failure (CHF), caused by administration of L-isoproterenol (2.5 mg/kg twice a day intraperitoneally for 21 days), promotes uncoupling of respiration and oxidative phosphorylation. The rate of mitochondrial oxygen consumption in the metabolic state V3 by Chance in animals with CHF decreased by 53.3% ($p < 0.05$) with malate using (as an oxidation substrate feeding \dot{N} -complex I of the electron transport chain (ETC)), by 70.6% ($p < 0.05$) with succinate using (\dot{N} -complex II substrate) and by 63.6% ($p < 0.05$) when malate and succinate were added simultaneously. The respiratory control ratio significantly decreased 2.3 times for \dot{N} -complex I, 2.5 for \dot{N} -complex II, and 2.6 times for the simultaneous operation of two respiratory chain complexes in mitochondria of CHF rats compared to intact animals. Mitochondrial dysfunction in experimental CHF is evidently due to the development of oxidative stress. It was revealed that the content of malonic dialdehyde (MDA) in the group of rats with experimental CHF was higher by 54.7% ($p < 0.05$), as compared with intact animals. The activity of superoxide dismutase (SOD) and catalase was lower by 17.5% ($p < 0.05$),

and by 18.4%, respectively than in the intact group. The dense extract from herba of *Primula veris* L. (DEHPV) 30 mg/kg limits the development of mitochondrial dysfunction in rats with experimental CHF, as evidenced by an increase in the role of V3 respiration for the first and second respiratory chain complexes in 1.7 ($p < 0.05$) and 2.0 times ($p < 0.05$), respectively, the ratio of respiratory control (RCR) $\hat{=}$ 1.7 times ($p < 0.05$) for \hat{N} -complex I and 2 times ($p < 0.05$) for \hat{N} -complex II compared with the negative control. The concentration of MDA was by 15.7% ($p < 0.05$), lower and the activity of SOD was by 56.3% ($p < 0.05$) higher.

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5. *Devyatov A.A., Fedorova T.N., Stvolinsky S.L., Ryzhkov I.N., Riger N.A., Tutelyan V.A.*

Study of the neuroprotective effects of carnosine in an experimental model of focal cerebral ischemia/reperfusion.

Oxidative stress is one of the key factors in brain tissue damage in ischemia, which indicates the appropriateness of using antioxidants under these conditions. One of the promising antioxidants for the therapy of ischemic stroke is the natural dipeptide carnosine. The neuroprotective effect of dietary carnosine administration was investigated in an experimental model of focal cerebral ischemia/reperfusion in Wistar rats. Animals received carnosine with a diet at a daily dose of 150 mg/kg for 7 days before temporary occlusion of the middle cerebral artery (MCA), performed for 60 min. At 24 h after the onset of ischemia the effect of carnosine on the area of the necrotic core was evaluated in animals. In brain tissue of animals the content of malondialdehyde (MDA), protein carbonyls (PC), total antioxidant capacity (TAC), total activity of superoxide dismutase (SOD), glutathione peroxidase (GP), catalase (CAT) and glutathione transferase (GT), content of isoprostanes and cytokines were measured. Carnosine significantly reduced the infarct size. Carnosine also increased TAC and reduced the level of MDA and isoprostanes in brain tissue. Influence of carnosine on other parameters was not detected. Thus carnosine consumed prophylactically with the diet for 7 days before the induction of ischemia by means of MCA occlusion in rats provides the direct neuroprotective effect, retains high antioxidant activity of brain tissue, reduces the level of oxidative damage markers (MDA and isoprostanes) but does not have any effect on the activity of antioxidant enzyme systems and production of cytokines in brain tissue.

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6. *Zinchuk V.V., Zhadko D.D., Gulyai I.E.*

Prooxidant-antioxidant balance depending on endothelial nitric oxide synthase G894T polymorphism.

The aim of the study was to assess the prooxidant-antioxidant balance depending on endothelial nitric oxide synthase G894T polymorphism. The frequency distribution of alleles and genotypes of G894T polymorphism, nitrite concentration, hydrogen sulphide, lipid peroxidation products (diene conjugates, malonic dialdehyde), antioxidants (reduced glutathione, catalase, ceruloplasmin, retinol) were determined in venous blood of healthy males. The incidence of the GG genotype was 49.1%, GT $\hat{=}$ 44.2%, TT $\hat{=}$ 6.7%. The level of malonic dialdehyde in erythrocytes with the GG genotype is 16.8% lower than in the genotype GT. The concentration of hydrogen sulphide in the blood with the GG genotype was 27.5 [18,2; 32,5] mM, GT $\hat{=}$ 28.6 [22.9; 33.8] mM, TT $\hat{=}$ 36.3 [33.8; 42.5] mM. The content of total nitrites in plasma with the GG genotype was 10.4 [9,0; 12,5] mM, GT $\hat{=}$ 10.4 [8,9; 11.8] mM, TT $\hat{=}$ 9.4 [8,8; 9,8] mM. The genotype GG causes a lower level of malonic dialdehyde in comparison with the heterozygous genotype. The G894T polymorphism allele T is associated with a low content of total nitrites in the plasma and a high concentration of hydrogen sulfide. The data obtained suggest that if the oxygen supply of the organism is impaired, the endothelial nitric oxide synthase G894T polymorphism may be important for the oxidative stress development.

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7. *Buneeva O.A., Kopylov A.T., Zgoda V.G., Medvedev A.E.*

The effect of deprenyl and isatin administration to mice on the proteomic profile of liver isatin-binding proteins.

Isatin (indol-2,3-dione) is an endogenous indole found in the brain, peripheral tissues and biological body fluids of humans and animals. Its wide spectrum of biological activity is realized via interaction with numerous isatin-binding proteins; these include proteins playing an important role in the development of neurodegenerative pathology. In the context of the neuroprotective effect, the effect of isatin is comparable to the effects of deprenyl, a pharmacological agent used for treatment of Parkinson's disease. In this study, the effects of the course of deprenyl (1 mg/kg) and isatin (20 mg/kg) administration for 21 days on the profile of the isatin-binding proteins of the liver of mice have been investigated. Proteomic profiling of liver isatin-binding proteins of control mice by means of 5-aminocaproylisatin as an affinity ligand resulted in identification of 105 proteins. Treatment of animals with a low dose of isatin slightly decreased (up to 91), while injections of deprenyl slightly increased (up to 120) the total number of isatin-binding proteins. 75 proteins were common for all three groups; they represented from 62.5% (in deprenyl treated mice) and 71% (in control mice), to 82% (isatin treated mice) of the total number of identified liver isatin-binding proteins. Proteomic analysis of the isatin-binding proteins of mice treated with isatin (20 mg/kg) or deprenyl (1 mg/kg) for 21 days revealed a representative group of proteins ($n=30$) that were sensitive to the administration of these substances. Taking into account the previously obtained results, it is reasonable to suggest that the change in the profile of isatin-binding proteins may be attributed to accumulation of isatin and deprenyl in the liver and interaction with target proteins prevents their subsequent binding to the affinity sorbent. In this context, the identified isatin-binding liver proteins of control animals that do not bind to the affinity sorbent (immobilized isatin analogue) after treatment of animals with either deprenyl or isatin appear to be specific targets directly interacting with isatin in vivo.

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8. *Dolgareva S.A., Sorokin A.V., Konoplya N.A., Bushmina O.N., Bystrova N.A., Ovod A.I.*

The use of immunomodulators, antioxidants and hepatoprotectors for the correction of the liver, erythrocytes and the immune system disorders in chronic ethanol intoxication.

The effectiveness of three various combinations of an immunomodulator with an antioxidant and a membrane protector in the correction of metabolic and immune disorders has been studied in the experiment under 60-days ethanol intoxication. The development of such biochemical syndromes of the liver damage as cytolysis, intrahepatic, intracellular cholestasis, toxic liver damage by necrotic type, insufficiency of synthetic processes and inflammatory has been revealed. Oxidative stress development and the activation of lipid peroxidation on the systemic (blood plasma) and local level

(erythrocytes) have been established. Suppression of adaptive immunity formation and phagocytic capabilities of neutrophils under the increase in their oxygen-dependent activity has been determined, which indicates the presence and possible progression of the inflammatory process at the systemic level. A disorder of erythrocytes metabolic activity, a decrease in stable metabolites of nitric oxide detected in blood plasma been revealed, indicating its uncompensated consumption, causing vasoconstriction and thrombosis, which can additionally arise due to the established increase in the prothrombin index. Combined use of *Longidasa*, *Mexicor*, *Essentiale forte N* or *Glutoxim*, *Mexidol*, *Heptral* and *Phosphogliv* was more effective in the correction of immune-metabolic disorders in chronic alcohol intoxication than *Hepon*, *Hypoxen* and *Phosphogliv*.

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9. Kopylov A.T., Tikhonova O.V., Farafonova T.E., Novikova S.E., Shushkova N.A., Shevchenko V.E., Liao Pao-Chi, Archakov A.I., Zgoda V.G.

Quantitative targeted screening of proteins associated with lung adenocarcinoma cancer by the method of selected reaction monitoring.

In the present study, we applied selected reaction monitoring (SRM) to a group of proteins that were previously reported to be associated with lung cancer (Novikova S.E. et al. (2017) *Biomeditsinskaya khimiya*, 63, 181-210. [1]). Measurements were performed on 59 plasma samples. These samples included: 23 samples of plasma of patients diagnosed with lung adenocarcinoma (LAC), 11 samples of plasma of patients diagnosed with squamous cell lung carcinoma (SqCC), 25 samples of donors with no previous history of oncological diseases, and one pooled sample from each of the above group. As a result of the SRM measurements 52 proteins were detected at least in one individual plasma sample. Statistical analysis showed that there were two groups confidently differentiated by the concentration value of 8 proteins wherein 5 proteins displayed increased level (P00738, P26639, P21926, P08603, P51149) in LAC group and 3 proteins (P51884, O15162, Q8N2K0) indicated diminishing the concentration level towards the control level. Data on protein concentrations obtained for LAC and SqCC did not distinguish the samples by statistical clustering analysis. These potential biomarkers can be used for further development of methods for early diagnostics of lung cancer.

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10. Bodienkova G.M., Boklazhenko E.V., Bodienkova S.G., Beygel E.A.

Comparative characteristics of cytokine and IgE levels in patients with bronchial asthma of professional and non-professional genesis.

A comparative evaluation of serum concentrations of cytokines and IgE production in patients with occupational bronchial asthma (BA) caused by exposure to the toxic-dust factor of the aluminum industry and patients with asthma of unprofessional genesis was carried out. A more pronounced pro-inflammatory response has been found in patients with occupational BA characterized by hyperproduction of IL-1b, IL-8. While for persons with non-professional asthma, a decrease in IL-1b, IL-5, IL-10 is characteristic. The common pattern of the detected changes in the patients of both groups consists in an increase in the production of IgE (6 times in patients with occupational BA and 8.9 times with non-occupational asthma) and a decrease in serum concentrations of TNF- α . Various cytokine manifestations in occupational and unprofessional BA may be associated with different etiopathogenetic mechanisms of disturbance of intra-immune regulation, and also confirms the professional conditionality of the revealed changes in patients with BA who work in the aluminum industry.

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