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1. Martyanov A.A., Kaneva V.N., Panteleev M.A., Sveshnikova A.N.

CLEC-2 induced signalling in blood platelets.

Platelet activating receptor CLEC-2 has been identified on platelet surface a decade ago. The only confirmed endogenous CLEC-2 agonist is podoplanin. Podoplanin is a transmembrane protein expressed by lymphatic endothelial cells, reticular fibroblastic cells in lymph nodes, kidney podocytes and by cells of certain tumors. CLEC-2 and podoplanin are involved in the processes of embryonic development (blood-lymph vessel separation and angiogenesis), maintaining of vascular integrity of small vessels during inflammation and prevention of blood-lymphatic mixing in high endothelial venules. However, CLEC-2 and podoplanin are contributing to tumor methastasis progression, Salmonella sepsis, deep-vein thrombosis. CLEC-2 signalling cascade includes tyrosine-kinases (Syk, SFK, Btk) as well as adapter LAT and phospholipase Cg2, which induces calcium signalling. CLEC-2, podoplanin and proteins, participating in CLEC-2 signalling cascade, are perspective targets for antithrombotic therapy.

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2. Vorontsova J.E., Cherezov R.O., Kuzin B.A., Simonova O.B.

Aryl-hydrocarbon receptor as a potential target for anticancer therapy.

Aryl-hydrocarbon receptor (Aryl Hydrocarbon Receptor, AHR) is a ligand-dependent transcription factor, whose functions are related to xenobiotic detoxification, response to inflammation, and maintenance of tissue homeostasis. Recent investigations suggest that AHR also plays an important role in the processes of carcinogenesis. Increased expression of AHR is observed in several types of tumors and tumor cell lines. In addition, it turned out that the composition of pharmaceutical drugs used in oncotherapy includes some ligands AHR. These facts allow us to consider an aryl-hydrocarbon receptor as a potential target for anticancer therapy, especially for the treatment of severe cancers whose treatment options are very limited or do not exist at all. In this review the examples of AHR ligands' effect on tumor cell cultures and on model mice lines with AHR-dependent response are discussed.

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3. Nazarenko M.S., Markov A.V., Sleptsov A.A., Koroleva I.A., Sharysh D.V., Zarubin A.A., Valiahmetov N.R., Goncharova I.A., Muslimova E.F., Kuznecov M.S., Kozlov B.N., Afanasiev S.A., Puzyrev V.P.

Comparative analysis of gene expression in vascular cells of patients with advanced atherosclerosis.

In this study we performed a comparative gene expression analysis of carotid arteries in the area of atherosclerotic plaques and healthy internal mammary arteries of patients with advanced atherosclerosis by using microarray HumanHT-12 BeadChip (â€œIlluminaâ€•). The most down-regulated genes were APOD, FABP4, CIDEC and FOSB, and up-regulated gene was SPP1 (|FC|>64; pFDR<0.05). The majority of differentially expressed genes were down-regulated in advanced atherosclerotic plaques. Unexpectedly, genes involved in immune and inflammatory responses were down-regulated in advanced atherosclerotic plaques to compare with the healthy arteries (arachidonic acid metabolism, cytokine-cytokine receptor interaction, NOD-like receptor signaling pathway, Jak-STAT signaling pathway, TNF signaling pathway). â€œCellular response to metal ionâ€• (metallothioneins) and â€œExtracellular matrix organizationâ€• were the most significant Gene ontology terms among the down- and up-regulated genes, respectively.

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4. Buneeva O.A., Gnedenko O.V., Medvedeva M.V., Ivanov A.S., Medvedev A.E.

The effect of the neuroprotector isatin on complex formation of beta-amyloid peptide fragments with some intracellular proteins.

Amyloid-Î² peptide (1-42) (AÎ²₁₋₄₂) is a key player in the development and progression of Alzheimerâ€™s disease (AD) and related pathologies, determined by formation of protein aggregates in the central nervous system. AÎ²₁₋₄₂ binding to crucial intracellular targets (and their subsequent inactivation) obviously represents one of the earliest events preceding extracellular pathogenic oligomerization/aggregation of AÎ²₁₋₄₂. It is reasonable to expect that dissociation of the AÎ²₁₋₄₂ complexes with intracellular proteins by means of inhibitors followed by subsequent degradation of AÎ²₁₋₄₂ would not only protect critically important proteins but also prevent intracellular accumulation of AÎ²₁₋₄₂. The aim of this study was to investigate the effect of the neuroprotector isatin (100 mM) on interaction of known AÎ²-binding proteins, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and pyruvate kinase, with AÎ²₁₋₄₂ and its fragments (AÎ²₁₋₂₈, AÎ²₁₂₋₂₈, AÎ²₂₅₋₃₅). AÎ²₁₋₄₂ and its fragments (AÎ²₁₋₂₈, AÎ²₁₂₋₂₈, AÎ²₂₅₋₃₅) immobilized on the Biacore optical biosensor chip interacted with GAPDH and pyruvate kinase. The lowest and basically equal Kd values were determined for GAPDH and pyruvate kinase complexes with immobilized AÎ²₁₋₄₂ and AÎ²₂₅₋₃₅. The presence of 100 mM isatin caused a significant (more than fivefold) increase in the Kd values for GAPDH complexes with all AÎ² peptides except AÎ²₁₋₂₈. In contrast to GAPDH isatin increased dissociation of pyruvate kinase complexes only with AÎ²₁₋₄₂ (causing a 30-fold increase in Kd) and to a lesser extent with AÎ²₁₂₋₂₈ and AÎ²₂₅₋₃₅ (a 10-fold increase in Kd). It should be noted that in the presence of isatin the Kd values for GAPDH and pyruvate kinase complexes with all AÎ² studied were in a narrower concentration range (10-7 M â€“ 10-6 M) than in the absence of this neuroprotector (10-8 M â€“ 10-6 M). Data obtained suggest existence of principal possibility of (pharmacological) protection of crucial intracellular targets against both AÎ²₁₋₄₂, and its aggressive truncated peptides (AÎ²₂₅₋₃₅).

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5. Avvakumova N.P., Kamilov F.H., Zhdanova A.V., Menâ€™shikova I.A., Zhernov Yu.V., Krivopalova M.A., Glubokova M.N., Katunina E.E.

The influence of humus acids of peloids and its components on free radical processes.

The effect of individual components of humic substances of peloid on free radical oxidation processes has been investigated under conditions of oxidative stress induced in albino rats. Biological activity of peloids was determined using such parameters as the general antioxidant activity, activity superoxide dismutases, catalases and glutathione peroxidases on the third and tenth day of the experiment. Results indicate that the state of oxidative stress can be corrected on the third day of the experiment. Humic acids restore not only normal physiological redox systems, but also increase the activity of antioxidant enzymes on the 10th day.

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6. Mikhalchik E.V., Maximov D.I., Ostrovsky E.M., Yaskevich A.V., Vlasova I.I., Vakhrusheva T.V., Basyreva L.Yu., Gusev A.A., Kostevich V.A., Gorbunov N.P., Sokolov A.V., Panasenko O.M., Gusev S.A.

Neutrophils as a source of factors that increase the length of the inflammatory phase of wound healing in patients with type 2 diabetes mellitus.

Oxidative stress and neutrophil activation leading to an increase in myeloperoxidase (MPO), elastase and neutrophil extracellular trap (NET) levels in blood are considered as pathogenic mechanisms responsible for the development of extremity damage in people with type 2 diabetes mellitus (T2DM). The aim of this study was to analyze the relationship between factors, associated with neutrophil activation, and the length of the initial phase of wound healing (the inflammatory phase) in T2DM patients. Patients were divided retrospectively into three groups depending on the damage extent: group 1 (wound on toe) < group 2 (wound on foot) < group 3 (wound on lower leg). Compared to the control group (healthy volunteers), T2DM patients at admission to hospital had significantly ($p<0.05$) increased levels of blood glucose and glycated hemoglobin (groups 1-3), ESR (groups 1 and 3), blood neutrophil count (groups 2 and 3), plasma MPO concentration (groups 1-3) and blood NET concentration (group 3) and decreased levels of plasma thiols (groups 1-3) and erythrocyte glutathione peroxidase activity (groups 2 and 3). The length of hospital stay after surgical procedures corresponded to the length of the inflammatory phase of the wound healing process and correlated with the number of blood neutrophils in patients before surgery ($r=0.72$, $p<0.05$). Leukocytic intoxication index depended on wound area ($r=0.59$, $p<0.05$), and it was significantly higher for groups 2 and 3 compared to the control group and group 1. The neutrophil count before surgery in T2DM patients with damage in the lower extremities correlated with the length of the inflammatory phase of wound healing. The correlation found can be attributed to an increase in extracellular MPO and NETs, which, in its turn, results from the activation and degranulation of neutrophils and netosis. Thus, the duration of the inflammatory phase of wound healing depends on specific aspects of systemic inflammation increasing oxidative/halogenative stress and intoxication.

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7. Drukker N.A., Durnitsyna O.A., Nikashina A.A.

The role of modification of innate immunity in development of premature labore.

To clarify the role of the infectious factor in the development of premature birth (PB) in women in serum, the content of TLR-4, the p65 subunit of the nuclear factor NF-kB, the cytokine TNF-a and the activity of PLA2 (phospholipase A2) were determinated by the enzyme immunoassay was studied. The profile of bioregulators in women with premature births was characterized by a high content of TLR-4, TNF-a and an increase in PLA2 activity and a decrease in the activity of the p65 subunit of NF-kB. 89 women aged 20-39 years were examined at 34-40 weeks gestation. They were divided into two groups: 42 women with preterm birth at 34-36.6 weeks, the control group is represented by 47 patients. The risk factors for PB are the presence of PB in history, endocervicitis, colpitis, dysbiosis, diseases of the urinary system (chronic pyelonephritis, chronic cystitis), aggravated obstetric and gynecological history (the threat of abortion during gestation, moderate preeclampsia, anemia of the pregnant woman). The obtained data of the studied bioregulators testify to the role of the infectious inflammatory process in the development of PB, which is evidenced by the high level of TLR-4, a component of innate immunity leading to the activation of the TLR-4 signaling pathway, which increases the activity of PLA2-factor of premature contractile activity of the uterus.

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8. Vulf M.A., Kirienkova E.V., Skuratovskaia D.A., Levada E.V., Volkova L.V., Zatolokin P.A., Gazatova N.D., Litvinova L.S.

Factors governing development of nonalcoholic fatty liver disease and insulin resistance in obesity.

The factors promoting development of non-alcoholic fatty liver disease in patients with obesity and different state of carbohydrate metabolism have been studied. 43 patients were examined; these included 26 patients with abdominal obesity (BMI=52.9Â±7.9 kg/m2). The control group consisted of 17 conditionally healthy donors without obesity (BMI=18.9-24.9 kg/m2), seven of them formed a comparison group that was included to compare the results of study on the levels of tissue-specific expression of HSP70 mRNA. The study of mRNA expression was performed by real-time PCR. The concentration of IL-6 and TNF-a was measured in blood serum by the ELISA method. In patients with obesity with diabetes mellitus type 2 (DM2), a significant increase in the serum level of proinflammatory cytokines was found in comparison with the group of patients without DM2 and control. The results of histological examination of liver biopsy specimens in obese patients revealed the most pronounced changes in the group of DM2 patients. Regardless of the stage of nonalcoholic fatty liver disease in obese DM2 patients, an increase in the area of fatty inclusions (relative to the group without type 2 diabetes) was recorded. The study of the HSP70 gene expression in peripheral blood mononuclear cells allowed its significant increase relative to the comparison group. The relationship between the level of expression of the HSP70 gene in metabolically active tissues (visceral, subcutaneous adipose tissue and liver) established in all obese patients with the serum content of proinflammatory cytokines (IL-6 and TNF-a) may indicate suppression of HSP70 expression in these tissues, background of systemic and local inflammation in obesity.

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9. Airapetov M.I., Sekste E.A., Eresko S.O., Bychkov E.R., Lebedev A.A., Shabanov P.D.

Chronic alcoholism influences the mRNA level of the orexin receptor type 1 (OX1R) in emotiogenic structures of the rat brain.

Orexin and its receptors were shown to be involved into mechanisms of pathological craving to alcohol. This paper demonstrates that the orexin receptor type 1 (OX1R) mRNA level significantly decreased in the prefrontal cortex of rats chronically (during 6 months) consuming ethanol compared with intact control. The same results were observed on day 1 and day 7 of alcohol withdrawal after chronic alcoholization. On the contrary, in the hippocampus, the OX1R mRNA level increased on day 1 and day 7 of alcohol withdrawal. In the ventral tegmental area, the OX1R mRNA level did not change on the day 1 and day 7 of alcohol withdrawal compared with the groups of chronic alcoholization and intact control. These findings point out involvement of the prefrontal cortex and hippocampus first of all in mechanisms mediating chronic alcohol intoxication. The ventral tegmental area is described as a typical dopaminergic structure providing the executive mechanism of emotion reactions connected with alcohol abuse in particular. It is possibe, that the modulating action of orexins on dopaminergic neurons in this structure does not provide a significant effect on control of emotion reactions in alcoholism.

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10. Boyko S.S., Zherdev V.P., Shevchenko R.V.

Pharmacokinetics of noopept and its active metabolite cycloprolyl glycine in rats.

The study of the pharmacokinetics of new drugs and the identification of active metabolites is a necessary step for effective and safe use in the clinical practice. It is especially important for peptide drugs due to their enzymatic instability, low bioavailability and poor permeability through the blood-brain barrier (BBB). The role of endogenous neuropeptides containing cyclic amino acids, proline, pyroglutamic acid, and glycine, in the regulation of memory processes is known as terminal peptide fragments. The development of nootropic drugs based on natural neuropeptides with high pharmacological activity and improved pharmacokinetic properties (enzymatic stability, high bioavailability, and good permeability through the BBB) is an important problem of modern neuropsychopharmacology. Developed drugs â€“ representing short (di- and tri-) peptides appear to meet these requirements. In the Zakusov Research Institute of Pharmacology a nootropic agent noopept (N-phenylacetyl-prolyl-L-glycine ethyl ester), was developed and introduced into medical practice, studies of its pharmacokinetics in ratsrevealed that the noopept metabolite found in the rat plasma and brain, cyclo-prolyl-L-glycine (CPG), differed significantly in its pharmacokinetic parameters from noopept, but at the same time it had similar noopept multi-component spectrum of pharmacological action, namely the influence on higher integrative functions of memory.

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