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1. Naryzhny S.N., Legina O.K.

Structural-functional diversity of p53 proteoforms.

Protein p53 is one of the most studied proteins. This attention is primarily due to its key role in the cellular mechanisms associated with carcinogenesis. Protein p53 is a transcription factor involved in a wide variety of processes: cell cycle regulation and apoptosis, signaling inside the cell, DNA repair, coordination of metabolic processes, regulation of cell interactions, etc. This multifunctionality is apparently determined by the fact that p53 is a vivid example of how the same protein can be represented by numerous proteoforms bearing completely different functional loads. By alternative splicing, using different promoters and translation initiation sites, the TP53 gene gives rise to at least 12 isoforms, which can additionally undergo numerous (>200) post-translational modifications. Proteoforms generated due to numerous point mutations in the TP53 gene are adding more complexity to this picture. The proteoforms produced are involved in various processes, such as the regulation of p53 transcriptional activity in response to various factors. This review is devoted to the description of the currently known p53 proteoforms, as well as their possible functionality.

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2. Danilenko E.D., Belkina A.O., Sysoeva G.M.

Development of drugs on the basis of high-polymeric double-stranded RNA for antiviral and antitumor therapy.

The review summarizes literature data on the development of drugs based on natural and synthetic high-polymeric double-stranded RNA, and their antiviral, immunoadjuvant and antitumor properties. Special attention is paid to cell receptors responding to exogenous dsRNA, the paths of dsRNA-dependent antiviral reaction, ability of dsRNA to inhibit growth and induce apoptosis ofmalignant cells. It has been shown that enhancing the innate immune response with dsRNA can be an effective component in improving methods for treating and preventing infectious and cancer diseases. The further use of dsRNA for the correction of pathological processes of different origin is discussed

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3. Novikova S.E., Vakhrushev I.V., Tsvetkova A.V., Shushkova N.A., Farafonova T.E., Yarygin K.N., Zgoda V.G.

Proteomics of transcription factors: identification of pool of HL-60 cell line-specific regulatory proteins.

HL-60 promyelocytic cells are a widely used as a model for studying induced granulocytic differentiation. Investigation of proteins of the nuclear fraction, particularly transcription factors, is necessary for a better understanding of molecular mechanisms of cell maturation. Mass spectrometry is a powerful tool for analyzing a proteome due to its high sensitivity, specificity and performance. In this paper, using the selected reaction monitoring (SRM) method, we have assessed the levels of RBPJ, STAT1, CEBPB, CASP3, VAV1, PRKDC, PARP1 and UBC9 nuclear proteins isolated using hypertonic buffer, detergents (sodium dodecyl sulfate (SDS), sodium deoxycholate (DOC) and fissionable detergent ProteaseMAXâ„¢) and using centrifugation in a sucrose density gradient. The minimum and maximum protein content was 1.13Â±0.28 and 14.34Â±1.63 fmol/mkg of total protein for the transcription factor RBPJ and ubiquitin-protein ligase type I UBC9, respectively. According to the results of shotgun mass spectrometric analysis of nuclear fractions, 2356 proteins were identified, of which 106 proteins were annotated as transcription factors. 37 transcription factors were uniquely identified in the fraction obtained by centrifugation in a sucrose density gradient, while only 9 and 8 transcription factors were uniquely identified in the nuclear fractions obtained using hypertonic buffer and detergents, respectively. The transcription factors identified in the HL-60 cell line represent regulatory molecules; their directed profiling under the influence of differentiation inducers, will shed light on the mechanism of granulocyte maturation.

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

A biosensor study of protein interaction with the 20S proteasome core particle.

It becomes increasingly clear that ubiquitination of cellular proteins is not an indispensable prerequisite of their degradation in proteasomes. There are a number of proteins to be eliminated which are not pre-ubiquitinated for their recognition by regulatory subcomplex of 26S proteasome, but which directly interact with the 20S proteasome core particle (20S proteasome). The obligatory precondition for such interaction consists in existence of disordered (hydrophobic) fragments in the target protein. In this study we have investigated the interaction of a number of multifunctional (moonlighting) proteins (glyceraldehyde-3-phosphate dehydrogenase (GAPDH), aldolase, pyruvate kinase) and neurodegeneration-related proteins (a-synuclein, myelin basic protein) with 20S proteasome immobilized on the SPR-biosensor chip and stabilized by means of a bifunctional agent dimethyl pimelimidate (in order to prevent possible dissociation of this subcomplex). Only two of all investigated proteins (aldolase and pyruvate kinase) interacted with the immobilized 20S proteasome (Kd of 8.17Â´10-7 M and 5.56Â´10-7 M, respectively). In addition to earlier detected GAPDH ubiquitination, mass spectrometric analysis of the studied proteins revealed the presence of the ubiquitin signature (Lys-e-Gly-Gly) only in aldolase. Oxidation of aldolase and pyruvate kinase, which promotes elimination of proteins via their direct interaction with 20S proteasome, caused a 2-3-fold decrease in their Kd values as comparison with this parameter obtained for the intact proteins. The results of this study provide further evidence for direct interaction of both ubiquitinated proteins (aldolase), and non-ubiquitinated proteins (pyruvate kinase) with the 20S proteasome core particle (20S proteasome). The effectiveness of this interaction is basically equal for the ubiquitinated proteins and non-ubiquitinated proteins.

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5. Pal`chikova N.A., Kuz`minova O.I., Selyatitskaya V.G., Afonnikova E.D.

Hypercorticism during streptozotocin diabetes and mifepristone administration: the role of cyclic adenosine monophosphate.

It was studed basal and ACTH-stimulated production of cyclic adenosine monophosphate (cAMP) and corticosteroid hormones (progesterone and corticosterone) in rat adrenals in vitro under streptozotocin diabetes, in conditions of mifepristone administration and their combination. It was shown that in streptozotocin diabetes animals, both the basal and adrenocorticotropic hormone (ACTH) stimulated cAMP production significantly increased; this was accompanied by the increase in basal and ACTH-stimulated progesterone and corticosterone production in rat adrenals in vitro. Repeated administration of mifepristone to control and diabetic rats caused an increase mainly in ACTH-stimulated production of the main glucocorticoid hormone, corticosterone, without additional changes in the cAMP level. The results obtained suggest activation of two mechanisms of steroidogenesis enhancement in experimental animals. In rats with streptozotocin diabetes, both basal and ACTH-stimulated activity of all stages of steroidogenesis increase, which is mediated by the increased formation of cAMP as second messenger mediating the ACTH action on adrenocortical cells. Prolonged administration of mifepristone to control and diabetic rats resulted in increased activity of only late stages of steroidogenesis with predominant elevation of synthesis of physiologically active hormone corticosterone without additional changes in cAMP production level.

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6. Sirota T.V.

Effect of the sulfur-containing compounds on the quinoid process of adrenaline autoxidation; potential neuroprotectors.

The superoxide-generating reaction of adrenaline autoxidation in an alkaline medium, used in vitro to identify the antioxidant properties of various compounds, simulates the complex multistep process of quinoid oxidation of catecholamines (CA) in the body. Sulfur-containing cysteine (Cys) and reduced glutathione (GSH), as well as oxidized glutathione (GSSG), have been shown to inhibit this process. The studied substances were considered as inhibitors of quinoid oxidation and are evaluated as antioxidants. The IC50 values for Cys and GSH were close to 7.5 mM. Inhibition by GSSG was weaker; represented approximately 50-70% of Cys and GSH. Other sulfur-containing compounds that differ in chemical structure, the amino acids taurine and methionine were ineffective. The interest in this model and the search for effective compounds acting on this reaction is associated with one of the mechanisms of the etiopathogenesis of Parkinson's disease (PD) discussed in the literature, which occurs when the biochemical transformations of dopamine CA and its quinoid oxidation process are violated. Cys, GSH and GSSG in the model system inhibit quinoid oxidation of adrenaline, as a result of which the formation of superoxide (O2 Â·-) is also inhibited. Experiments with the superoxide-generating enzymatic reaction xanthine xanthioxidase, the chemistry of which is different and not related to formation of quinoid metabolites, showed that the studied substances did not inhibit O2 Â·- formation in this model. Thus, it was established that the biologically active sulfur-containing compounds Cys, GSH and GSSG are specific inhibitors of quinoid oxidation of CA, and are likely to be able to play the role of a neuroprotector. It is proposed to use these compounds in the treatment and prevention of PD by activating their biosynthesis in the body.

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7. Panada J.U., Faletrov Y.V., Frolova N.S., Shkumatov V.M.

Synthesis and evaluation of N-alkynylaminosteroids as potential CYP450 17A1 inhibitors.

Four isomeric dehydroepiandrosterone- and pregnenolone-based N-alkynylaminosteroids were synthesized and tested in vitro for inhibition of heterologously expressed CYP17A1. The highest inhibitory activity was observed when the optimal number of side chain atoms was met. The conjugate based on pregnenolone containing an N-propynyl moiety was found to interefere with enzymatic activity most effectively and consistently in the micromolar range.

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8. Brazhnikov D.A., Popova T.N., Kryl`skii E.D., Shulgin K.K., Matasova L.V., Shikhaliev H.S., Popov S.S.

Effect of 6-hydroxy-2,2,4-trimethyl-1,2-dihydroquinoline on the intensity of free radical processes and the activity of oxidative metabolism enzymes under toxic liver injury in rats.

The effect of 6-hydroxy-2,2,4-trimethyl-1,2-dihydroquinoline on markers of hepatocytes cytolysis (aspartate aminotransferase, alanine aminotransferase and gamma-glutamyl transpeptidase), parameters reflecting the state of oxidative status (intensity of biochemical luminescence and the content of diene conjugates), and the activity of oxidative metabolism enzymes (aconitate hydratase, glucose-6-phosphate dehydrogenase, NADP-isocitrate dehydrogenase) was studied in rats with CCl4-induced liver injury. The results obtained in the course of the work demonstrated the ability of the test compound to reduce the severity of oxidative stress and liver cells damage, as well as to change the activity of aconitate hydratase and NADP-generating enzymes in the direction of control values. 6-hydroxy-2,2,4-trimethyl-1,2-dihydroquinoline was more effective in normalizing CCl4-induced changes of the analyzed parameters that Carsil used as a reference compound. The tendency to normalize the state of oxidative status and enzyme activity of oxidative metabolism can attributed to hepatoprotective and antioxidant properties of the tested compound.

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9. Litvinova L.S., Shupletsova V.V., Yurova K.A., Khaziakhmatova O.G., Todosenko N.M., Malashchenko V.V., Shunkin E.O., Melashchenko E.S., Khlusova M.Yu., Komarova E.G., Chebodaeva V.V., Sharkeev Yu.P., Ivanov P.A., Khlusov I.A.

Secretion of niche signal molecules in conditions of osteogenic differentiation of multipotent mesenchymal stromal cells induced by textured calcium phosphate coating.

Secretion of 21 cytokines, chemokines and growth factors (LIF, SCF, SDF-1a, SCGF-b, M-CSF, MCP-3, MIF, MIG, TRAIL, GRO-a; IL-1a, IL-2ra, IL-3, IL-12(p40), IL-16, IL-18, HGF, TNF-b, b-NGF, IFN-a2, CTACK) has been studied in vitro in the culture of human adipose-derived multipotent mesenchymal stromal cells (hAMMSCs) in conditions of its osteogenic differentiation caused by 14-day contact with calcium phosphate (CP) surface with different roughness. Bilateral X-ray amorphous CP coatings were prepared on the samples of commercially pure titanium in the anodal regime using a micro-arc method. An aqueous solution prepared from 20 wt% phosphoric acid, 6 wt% dissolved hydrohyapatite nanopowder (particle diameter

10-30 nm with single agglomerates up to 100 nm), and 9 wt% dissolved calcium carbonate was used to obtain CP coating. hAMMSCs isolated from lipoaspirate were co-cultured after 4 passages with the CP-coated samples at final concentration of 1.5Â´105 viable karyocytes per 1.5 mL of standard nutrition medium (without osteogenic stimulators) for 14 days (a determination of [CD45,34,14,20], CD73, CD90 Ð¸ CD105 cell immunophenotype; an analysis of secretory activity) and 21 days (alizarin red S staining of culture) with medium replacement every 3-4 days. Under conditions of in vitro contact with rough CP coating hAMMSCs differentiated into osteoblasts synthesizing the mineralized bone matrix; this was accompanied by 2-3-fold increasing ratio of [CD45,34,14,20]+ hemopoietic cells. The following humoral factors of hemopoietic niches acted as the signal molecules escalating in vitro the hemopoietic base in 14 days of differentiating three-dimensional culture of hAMMSCs: either leukemia inhibitory factor (LIF) and stem cell factor (SCF) cytokines under mean index of CP roughness Ra=2.4-2.6 mm or stromal derived factor-1 (SDF-1a, CXCL12 chemokine) under Ra=3.1-4.4 mm.
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10. Zamorina S.A., Timganova V.P., Litvinova L.S., Todosenko N.M., Bochkova M.S., Shardina K.Y., Khramtsov P.V., Rayev M.B., Chereshnev V.A.
The role of alpha-fetoprotein in regulation of the cytokine profile of activated T-helpers and their conversion in Th17 phenotype.
We studied the effect of the native (non-recombinant) alpha-fetoprotein (AFP) on differentiation, proliferation, and cytokine profile of activated helper T cells 17 (Th17). The object of the study was a culture of isolated by immunomagnetic separation helper T cells (CD4+), induced into the Th17 phenotype by using TCR-activator and proinflammatory cytokines (IL-1Î² and IL-6). AFP had not significant effect on the frequency of Th17 cells (ROR-Î³Ï„+) in the helper T cell culture, and did not affect proliferation of these cells, as measured by Ki-67 expression. Evaluation of the cytokine profile of culture supernatants by using the Luminex xMAP technology, revealed that AFP did not affect the levels of IL-4, IL-5, IL-7, IL-8, IL-10, IL-17, IFN-Î³ and TNF-Î±, but at concentrations of 50 IU/ml and 100 IU/ml it increased IL-2 production by activated helper T cells. At the same time, AFP suppressed the synthesis of G-CSF and GM-CSF (10 IU/ml), but stimulated the production of CCL4/MIP-1Î² (100 IU/ml) and CCL2/MCP-1 chemokines (10 IU/ml and 50 IU/ml).
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