MOLECULAR PROFILING OF PROSTATE TUMORS
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Prostate cancer is a very heterogeneous disease [1]. Upon cancerogenesis, not only prostate epithelial cells are altered, but also stromal elements. Growing tumors are capable to change their microenvironment to avoid immune surveillance and to grow and proliferate [2]. To understand cancer development, it is necessary to investigate both, the tumor cells and the composition and characteristics of the tumor microenvironment [3]. This is important for diagnostics, prognosis and for the choice of an effective patient treatment, making the basis of personalized medicine. Aim: To analyze an expression pattern of the prostate cancer-associated genes (PCAG) and genes - markers of tumor microenvironment (TM); and to examine a putative correlation between gene expression and clinical characteristics, to define the molecular subtypes of prostate cancer and form a basis for the molecular profiling of prostate cancer.

Materials and Methods. Relative gene expression (RE) of 56 PCAG and TM markers were analyzed by a quantitative PCR in 37 prostate cancer tissues (T) of different tumor stages and Gleason scores (GS), 37 corresponding (paired) conventionally normal prostate tissues (N) and in 20 samples of benign prostate tumors (adenomas (A).

Results. We have found 30 differentially expressed genes in T compared with A. Among them there were cancer-related and prostate specific genes (AR, KRT18, MMP9, PTEN, TMPRSS2/ERG, VIM, ESR1, GCR, PDL1, PRLR, SRD5A2, VDR), 3 genes of IncRNA [PCA3, SCHLAP1, HOTAIR], several genes characterizing the state of tumor microenvironment [fibroblasts, lymphocytes, macrophages] [Thy1, CXCL12, CXCL14, CTGF, HIF1A, FAP, IFNβ1, CTLA4, IL1RL1, IL1R1, CD163, CCR4, CCL17, CCL22, NOS2A]. It was found 29 of 56 genes with significant RE correlations in T with clinical and pathological characteristics (GS, stage, PSA level, age). We have found some specific RE changes in groups with the presence of TMPRSS2/ERG fusion and different expression of PTEN. For examples, KRT18, PCA3 and SCHLAP1 genes showed significant differences in RE in adenocarcinomas with the fusion. In adenocarcinomas without the fusion, such properties were shown by the AR (2 isoform), MMP9, PRLR the HOTAIR genes. The ESR1 and SRD5A2 gene expression was altered in both types of adenocarcinomas Using the clustering procedures, we could cluster adenocarcinomas in three molecular subtypes, according to gene expression profiles of PCAG. A specific expression subtype of prostate tumors is characterized by the activated ERG signaling, due to the presence of TMPRSS2/ERG fusion, and also by high levels of the AR, PRLR, IGF, INS and PCA3.

The obtained results make the basis for the molecular profiling of prostate tumors to stratify tumors on specific molecular subtypes. It could help in diagnostic and prognosis of a course of disease. Further experiments are needed to confirm these data in a larger patient cohort and to propose a panel of oncomarkers for prostate cancer.

References:

Key words: relative gene expression patterns, prostate cancer, tumor molecular characteristics, tumor microenvironment, oncomarkers.

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ALPHA-FETOPROTEIN OF UMBILICAL CORD BLOOD AS A PREDICTOR OF LIFE DYSFUNCTION IN NEWBORN INFANTS WITH PERINATAL PATHOLOGY
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When risk factors are realized against the background of pathological birth stress, the functions of regulatory systems are violated in the newborn’s body, which leads to a disruption in the functional state of organ systems, in particular, the liver, causing disturbances in homeostasis. The development of pathological changes in the liver of newborns can be related both to the direct action of hypoxia on the fetal body in utero, and to be the result of a combined effect of the factors of antenatal and perinatal risk. [1] One of the essential features of the metabolism in the early stages of ontogenesis is the synthesis of embryospecific proteins such as fetoproteins. The main role in this process is played by trophoblast cells; after birth, the main synthesis of fetoprotein is carried out by the liver. Alpha-fetoprotein (AFP) is an embryo-specific protein with a molecular weight of about 70,000 D, resembling serum albumin by its physico-chemical properties,
placed between albumin and alpha-1-globulin in electrophoresis. During pregnancy, AFP is synthesized mainly by cells of the embryonic liver and yolk sac, to a lesser extent - in the gastrointestinal tract, lungs and bones of the fetus. Its first traces appear simultaneously with the onset of embryonic hematopoiesis in early-term fetuses. AFP is excreted from the body of a child up to 2 years [2]. AFP is a multifunctional protein with selective cellular stimulating and inhibitory activity. The binding of AFP to specific receptors on the cell membrane triggers the growth or proliferation of cells or affects the processes of their differentiation. The manifestations of AFP activity are partly related to its transport protein properties, capable of forming complexes with polyunsaturated fatty acids, bilirubin, pectins, some steroid hormones, and other biologically active ligands. AFP provides transport through membranes by interacting with high-affinity AFP-receptors of target cells of biologically active substances, which leads to activation of metabolism in tissues. In vitro, AFP decreases the activity of natural killers. Its participation in the metabolism of steroid hormones has been proved, due to which it plays an important role in the regulation of fetal growth and differentiation of fetal tissues, the protection of the fetus and the mother from the attack of immune systems and in limiting the influence of the mother's hormones, in particular estrogens, on the fetus [2-6]. The purpose of this work was to study the informative value of AFP umbilical cord blood as a predictor of liver failure in newborn babies with signs of severe perinatal pathology in the early neonatal period.

Materials and Methods. A comprehensive survey of 203 newborns has been conducted. The first group of the study consisted of 121 persons with a diagnosis of severe perinatal pathology; the second group of the study included 82 healthy newborn babies. Comprehensive biochemical analysis of blood serum (total protein, albumin, total bilirubin, glucose, urea, cholesterol and glycerides, alanine aminotransferase (ALT) activity, aspartate aminotransferase (AST), lactate dehydrogenase (LDH)) was performed using the "ULTRA" analyzer of the "Kone" company (Finland, company reagents) and the apparatus for electrophoresis "PARAGON" of the "Bekman" company (Austria, company reagents). Detection of AFP level in umbilical cord blood was performed using "Sandwich" immunoluminescence assay: MAGLUMI test for revealing the concentration of alpha-fetoprotein by chemiluminescence assay ("SNIBE", PRC). The obtained data were statistically processed by means of the programs Statistica 7.0 (StatSoftInc., USA) and MedCalc Software (Version 16.1). The results of each group are expressed as mean (M) and standard error (m) for symmetric distribution. The normality of data distribution was tested using Shapiro-Wilks test for sample size ≥ 30. To compare continuous variables parametric tests (independent t test) were used. The difference of the parameters was considered to be statistically significant with р<0.05. In the case of data were available, 2 × 2 tables were compiled to derive relative and absolute risk, odds ratio and quality parameters such as sensitivity (Se) and specificity (Sp) of AFP, respectively.

Results. The study groups did not differ in gestational age, anthropometric indicators and gender characteristics. The main clinical diagnosis in children of the I study group was severe asphyxia (19.0%), moderate asphyxia (41.3%), hemolytic disease of newborns (17.5%), neonatal sepsis (11.1%), neonatal encephalopathy (9.5%), congenital pneumonia (1.6%). In this group of children, the score on the Neonatal Therapeutic Intervention Scoring System (nTISS) scale was more than 20 points. The children underwent treatment in the Neonatal Intensive Care Unit (NICU). Newborns of the II group had a compensated state at birth and during the early neonatal period were provided with rooming-in care receiving exclusive breastfeeding. No child of this group had any manifestations of neonatal jaundice. Patients NICU, consisted the I study group, had the following manifestations of hepatic insufficiency: hepatomegaly (66.9%), splenomegaly (11.6%), jaundice (13.2%), hemorrhagic syndrome (14.9%), edematous syndrome (65.2%), acholic stool (5.8%), anemia syndrome (19.8%), hypoglycemic syndrome (62.8%). Clinical manifestations of severe perinatal pathology and hepatic failure in newborns were associated with statistically significant levels of liver dysfunction markers in serum. Thus, the level of total bilirubin in children of the I study group was 98.2 ± 9.57 μmol / l, in healthy newborns - 33.9 ± 2.16 μmol / l, p <0.05. The sensitivity of the AFP level in the umbilical cord

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THE EFFECT OF BISOPROLOL ON DISEASE COURSE FOR PATIENTS WITH HIGH SST2 LEVELS AND ACUTE MYOCARDIAL INFARCTION

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Data received in recent years confirm the SST2 value as a cardiac biomarker. Research of patients with heart failure demonstrated the SST2 role as independent mortality predictor for patients with severe congestive heart failure or acute heart failure. [3, 4, 5]. Taking into consideration sympathoadrenal system activation in patients with acute myocardial infarction (AMI), it is interesting to investigate beta-blockers (BB) therapy and its probable influence on disease course according to initial SST2 levels. The BB use for patients with AMI reduces left ventricular (LV) remodeling processes intensity and improves LV hemodynamic function, that decreases the area of myocardial infarction (MI) and duration of treatment [2]. Objective of the study is assessing of different bisoprolol doses effect on the incidence of adverse events for patients with AMI depending on the initial SST2 level.

Materials and Methods. 103 patients with ST-elevation myocardial infarction (STEMI) were included, 75 (72.8%) of them were men and 28 (27.2%) were women. Average age was (61.85±12.23) years old. All the patients underwent standard clinical and biochemical analysis in the first 24 hours. SST2 level was detected by enzyme linked immunoassay with the use of reagent kit «Presage ST2 Assay», Critical Diagnostics (the USA). Echocardiography was performed after patients admission to the hospital and after 6 months. Also all patients were going on six minute walk test (6MWT) for assessment of exercise tolerance. The cohorts of patients were divided according to initial SST2 level on admission to the hospital. SST2 distribution threshold was 35 ng/ml. This is the biomarker level, that has been proven in fundamental research [1]. First group with SST2 level < 35 ng/ml, was consist of 47 patients, and second group with SST2 level ≥ 35ng/ml, was consist of 56 patients. The combined endpoint was fatal event and hospitalization for decompensation of chronic heart failure or acute heart failure. Observation period for patients was 6 month. Subsequently 83 patients, who have no contraindications, were added to treatment BB, bisoprolol. Initial dose of the drug was 2.5 mg per day, with further increasing in the hospital and ambulatory. In one patients group the daily dose remained unchanged (2.5 mg) in connection with non-compliance of patients, in the second group it was possible to reach the target dose 5-10 mg. 40 patients with daily bisoprolol dose 2.5 mg were included to the first subgroup, 43 patients were included to the second subgroup with daily bisoprolol dose 5-10 mg.

Results. Outgoing SST2 blood serum level was 26.38 [20.96; 29.56] ng/ml in the first clinical group and 56.14 [44.83; 115.25] ng/ml in the second group (p< 0.001). The analysis revealed reliable SST2 level dependence on end systolic volume (p=0.025), left ventricular ejection fraction (LVEF) (p=0.007) and systolic blood pressure (p=0.006). In 6 months in the first group was significant increasing of SST2 blood serum level from 26.38 [20.96; 29.56] ng/ml to 63.36 [26.30-102.46] ng/ml (p<0.002), and heart rate deceleration (p=0.004), decreasing of systolic blood pressure (p=0.0001), and diastolic blood pressure (p=0.005). In the second group with initial high SST2 level (≥ 35 ng/ml) was less significant increasing of the biomarker from 56.14 [44.83-115.25] ng/ml to 100.09 [41.89-137.07] ng/ml (p=0.656) and reliable heart rate deceleration (p=0.001). Despite of the treatment, significant changes of LVEF and exercise tolerance were not determined in 6 months. The using low and target bisoprolol doses for patients with myocardial infarction with initial SST2 level (< 35 ng/ml) during 6 months was not associated with improvement of contractile myocardium function and functional state by going on 6MWT and also prevention of significant biomarker increasing. SST2 level increased from 25.99 [19.25-31.16] ng/ml to 40.28 [20.63-232.04] ng/ml (p=0.032) on the background of low bisoprolol dose and from 25.16 [21.75-28.54] ng/ml to 60.41 [29.26-123.20] ng/ml (p=0.051) on the background of high bisoprolol dose.

References:

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