indicate that MSC has both stimulating and suppressive actions on experimental neoplasms. We have shown previously that a single MSC administration to tumor-bearing animals has an oncomodulating effect on the growth of tumors. Short-term stimulation of the growth of tumor nodes initially after the MSC injection was usually followed by subsequent deceleration of their growth.

Here, we have studied the effects of allogeneic MSC on sarcoma M-1 in rats. On day 11 after the sarcoma M-1 implantation, 1.5 million MSC grown from the bone marrow cell population of Wistar rats was administered into the tail vein of outbred rats from the experimental group. On days 17 and 30 of the tumors growth, 10 rats from each group were used to study the sarcoma M-1. To analyze the MSC distribution and localization in the tumor parenchyma, on days 11 and 13, five rats in the study were intravenously infused 2 million MSC, labeled in vitro by bromodeoxyuridine (BrdU). The techniques for studying of the tumor reaction on the systemic MSC transplantation included immunostaining for PCNA, BrdU and PECAM-1, in conjunction with computerized analysis of the microscopic images.

One day after transplantation, the BrdU-labeled MSC localized in the perivascular areas of angiogenesis on the periphery of tumor nodes with the diameter of more than 6 mm, containing foci of spontaneous necrosis. Sometimes, labeled cells could be seen near the vessels situated deep in the tumor parenchyma. On day 3, cells with the low-intense BrdU immunostaining were found only rarely and mostly perivascularly. These cells were visualized in the region of pericytes' localization, and the low BrdU-immunostaining intensity of their nuclei indicated the label dilution effect.

Six days after the MSC administration, some local areas of the connective tissue enlargements on the periphery of tumor nodes were observed with a distinct vascular ingrowth into the tumor parenchyma. In the same areas, the marginal region of tumor nodes contained a considerable number of neutrophils and lymphocytes. The PCNA staining revealed foci of increased proliferative activity of tumor cells in these areas, as well as intensive proliferation of fibroblasts and vascular endothelium, which indicates the increase of angiogenesis and stroma formation. After the MSC administration the content of parenchyma with PCNA-positive nuclei significantly increased, whereas the volume fraction of the necrosis regions decreased by more than 1.5 times.

On day 30 of the sarcoma M-1 growth, tumors in the experimental group rats were surrounded by layers of connective tissue. The peritumoral area was infiltrated by numerous lymphocytes and macrophages. In the terminal period of the sarcoma growth, the most quantitative parameters for tumors in the experimental group did not significantly differ from the data obtained in the control group. Only the rate of tumor cell apoptosis in animals with transplanted MSC was statistically higher than that in control rats.

Reviewing the literature regarding the influence of MSC on the malignant growth revealed that this problem still remains quite unclear and disputable. One of the contradictions is their ability to have opposite effects on the repopulation activity of tumor cells. The complex interactions between MSC, tumor microenvironment and neoplastic cells seem to be crucial for the outcome of the oncological process development. Further detailed studies of the mechanisms of the cellular therapy using MSC on carcinogenesis are necessary to generate new insights into this area.

http://dx.doi.org/10.1016/j.ejcsup.2015.08.120

P34

Plasma micro-RNAs as noninvasive biomarkers for diagnostics of lung cancer

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Lung cancer (LC) is currently the world's leading cause of cancer-related mortality with overall mortality to incidence ratio of 0.87. Only 15% of LC patients are diagnosed at early stage of disease and have 5-year survival rate of 54%, whereas 56% of patients have distant metastases and 5-year survival rate of about 4%. Current methods of lung cancer diagnostics are not efficient as screening tools due to high costs (CT), low sensitivity and health risks (radiology), invasiveness (biopsy) or low prevalence in population (genetic alterations). New strategies for preclinical lung cancer screening as well as monitoring of post therapy relapses are required. MiRNAs circulating in blood were shown to reflect the progression of disease and are thus considered as potential biomarkers for cancer diagnostics and theranostics.

In this study we investigated seven-miRNA signature circulating in plasma of lung cancer patients and healthy individuals. All seven miRNAs were previously shown to be involved in either regulation of cell cycle and apoptosis and/or tumor development, invasion and vascularization.

Blood samples of 50 healthy individuals were obtained from Center of New Medical Technologies (Novosibirsk, Russia) and Novosibirsk Research Institute of Circulation Pathology of E.N. Meshalkin (Novosibirsk, Russia). Samples of 75 lung cancer patients, including 52 patients with squamous cell carcinoma (SCC) and 18 patients with adenocarcinoma (AC) were obtained from Novosibirsk Research Institute of Circulation Pathology of E.N. Meshalkin (Novosibirsk, Russia) and Tomsk Cancer Research Institute RAMS (Tomsk, Russia). None of the patients have undergone surgical treatment or received chemotherapy prior to blood collection. Lung biopsy specimens and imaging techniques were applied to confirm the histopathological features and tumor stages of LC patients. Study was approved by ethical committees of all participating organizations and written informed consent was provided by all participants.

Circulating miRNAs were isolated from blood plasma using a single-phase phenol-free protocol (Zaporozhchenko et al., Anal Biochem, 2015; Rus. patent application No. 2014137763, priority date 17.09.2014). Concentrations of miRNAs (miR-21, miR-19b,

miR-126, miR-25, miR-205, miR-183, miR-125b) were measured by qRT-PCR and normalized to miR-16.

Concentrations of four miRNAs (miR-19b, miR-21, miR-25, miR-183) were significantly different in lung cancer versus healthy individuals ($p<0.05$, T-test, two-sided). Two miRNAs were upregulated (miR-19b, miR-21), two were downregulated (miR-25, miR-183) in cancer patients. Four miRNAs (miR-19b, miR-126, miR-25, miR-205) were found to be differentially regulated in SCC patients when compared to healthy controls. In AC patients only two miRNAs (miR-19b, miR-183) were differently expressed. Thus, cancer subtypes have different input into overall picture.

Receiver Operating Characteristic (ROC) curve analysis of differentially expressed miRNAs in total study population and subtype-based groups showed that miR-19b has highest predictive value for total population and SCC patients, while miR-183 was more effective in discriminating patients with AC. All miRNAs except miR-21 showed strong bias towards one of the subtypes. Presumably a combination of miRNAs with opposite bias should provide a more potent diagnostic tool for cancer detection in total population than individual miRNAs or panels of miRNAs that are specific to one cancer subtype. Indeed, stepwise binary logistic regression has identified the combination of miR-19b and miR-183 to be a strong prediction of disease in total population and yielded a solid increase in AUC: 0,990 (miR-19b+miR-183) versus 0,806 (miR-19b) or 0,924 (miR-183). This combination can be used to identify lung cancer with 94.7% sensitivity and 95.2% specificity.

Thus, biological aspects such as tumor genetics and phenotype, stage of disease, response to therapy, and other meaningful tumor properties of such heterogeneous malignancies as LC can interfere with contents and composition of cell-free miRNA pool. Wide profiling of circulating miRNAs will specify biomarkers of LC phenotypes and improve non/less-invasive LC diagnostics.

http://dx.doi.org/10.1016/j.ejcsup.2015.08.121

A84

Polymorphic markers Arg72Pro and Gln157Lys of TP53 gene in nonsmall cell lung cancer

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The development of individual medicine is a very important part of the whole health care system and especially of the oncology patients' treatment. The predictive markers could help to prevent the development of the different diseases. Individual risk assessment is based on the study of polymorphisms in genes specific to different pathologies, especially those with a significant social impact, such as lung cancer.

Like many other cancers, lung cancer is a multi-factorial disease. The tumor suppressor genes are important in its pathogenesis. One such very important gene is TP53, which encodes the p53 tumor suppressor protein. It regulates the activation of specific cellular processes and signaling pathways involved in regulation, recognition of signals inside the cell, coordination of metabolic processes, genome repair, cell division and death (apoptosis), and interactions between cells. Insufficient production or property modification of this protein leads to the development of serious diseases, including lung cancer.

The TP53 gene has a number of polymorphic markers; the Arg72Pro and the Gln157Lys markers are very important in case of lung cancer. They are located in the DNA-binding domain of TP53 at exons that play essential structural and chemical roles in the contact between the p53 protein and specific DNA sequences that constitute the p53 response elements. These mutations result in a significant loss of DNA-binding activity and transactivation capacity (P. Hainaut and M. Hollstein, 2000).

We studied the association of polymorphic markers Arg72Pro and Gln157Lys of TP53 gene with the risk of nonsmall cell lung cancer (NSCLC) in patients from the Moscow region. Our study included 88 patients with NSCLC, 160 healthy persons as a control for Arg72Pro and 60 healthy persons as a control for Gln157Lys. We used PCR-RLFP analysis to identify the alleles of the polymorphic markers.

We observed higher frequencies of the markers predisposition genotypes in group of patients then in control group. The distribution frequency of Pro/Pro genotype Arg72Pro marker was 0.307 in the group of patients and 0.075 in the control. For the Gln157Lys marker the Lys/Lys genotype was not observed. The frequency of Gln/Lys genotype Gln157Lys marker was 0.377 in patients and 0.106 in the control. We found the association of both markers with the risk of NSCLC development. The genotype Pro/Pro of Arg72Pro marker showed the increasing of NSCLC risk: OR = 5.46, $p = 8 \times 10^{-6}$. The presence of Gln/Lys genotype of Gln157Lys marker also led to increased risk of cancer development: OR = 5.10, $p = 0.002$.

Our results suggest the importance of studied polymorphic markers for risk of NSCLC assessment. The status of the Arg72Pro and the Gln157Lys markers of TP53 gene can serve as an independent prognostic indicator in this type of cancer.

http://dx.doi.org/10.1016/j.ejcsup.2015.08.122

A84a

Role of BRCA1 dysfunction in sporadic triple-negative breast cancer

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Background: There is increasing evidence that BRCA1-related DNA-repair defects determine sensitivity to certain agents, such as platinum-based chemotherapy. There is a lot of evidence about a link between TNBC and BRCA1 deficiency. Many clinical characteristics and molecular features are shared by sporadic triple-negative breast cancer and BRCA1-associated breast cancer. The majority of BRCA1-related breast cancers are of basal-like/triple-negative phenotype. Identification of specific