Fund "Nauka" Project № 19004 Resume – Competition-Based Session 2019:
"Analysis of immunohistochemical expression level of markers for necroptosis in breast cancer"
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The **purposes** of the current project proposal are:

❖ Comparative research of expression level of Receptor-interacting protein kinase 3 (RIPK3) as a marker for necroptosis in patients with metastatic and non-metastatic breast cancer;

❖ Investigation of its predictive and prognostic value;

❖ Correlation analysis between RIPK3 expression in the primary tumor of different breast cancer subtypes and ER (estrogen), PR (progesterone), HER2 status, sex and age.

Based on the above-mentioned purposes, the following **objectives** are set:

1. Comparative research of immunohistochemical expression level of RIPK3 in the primary tumor of patients with breast cancer.
2. Correlation analysis between immunohistochemical expression level of RIPK3 and clinical-pathologic characteristics of patients with breast cancer.
3. Investigation of the predictive potential of RIPK3 expression in the primary tumor for response to endocrine therapy.
4. Analysis of the prognostic potential of RIPK3 expression in the primary tumor in relation to patient survival.

To achieve the **aims** and **objectives**, breast cancer biopsies will be selected. The cases will be divided into three groups dependent on their molecular classification, defined on the basis of ER, PR, HER2 and KI67 expression of tumor cells, as following: triple negative, HER2 positive and ER positive. RIPK3 expression will be evaluated in all of the cases. Different coloring procedures and statistical methods will be used for assessment of indices.

The expected results are related to establishment of factors, influencing the initiation, progression and metastasis, which could be used as "targets" in targeted therapy.

Expected results:

1. Breast cancer, at the time of diagnosis, is most often found between the ages of 61 and 70 years, in most cases is in the T2 N0 stage, shows a moderate degree of differentiation and high Ki67.
2. After adjuvant hormone, radiation and/or chemotherapy and remission, the median progression-free survival of breast cancer patients is 113.8 months.
3. Cytoplasmic expression of RIPK3 in mammary carcinoma tumor tissue is lower, while nuclear expression is higher than in the control group.
4. The cytoplasmic expression of RIPK3 in lobular carcinoma is higher than in ductal carcinoma.

5. Cytoplasmic RIPK3 expression is lowest in triple-negative carcinomas.

6. Cytoplasmic expression of RIPK3 in mammary carcinoma tumor tissue did not indicate dependence on patient age, T-stage, tumor spread (metastasis), tumor HER2 status, and was not associated with patient survival.

7. Highly differentiated mammary carcinomas have higher values of cytoplasmic expression of RIPK3 compared to tumors with a low degree of differentiation.

8. Intense cytoplasmic expression of RIPK3 in breast cancer occurs at pronounced intensity and high total score of ER, at expressed expression by area and intensity and high total score of PR and at low expression of Ki67.

9. Nuclear expression of RIPK3 in mammary carcinoma tumor tissue did not show dependence on patient age, histological type of carcinoma, T-stage, and degree of tumor differentiation.

10. With high nuclear expression of RIPK3 in tumor cells, the tumor is more likely to have lymph node metastases.

11. Nuclear expression of RIPK3 in mammary carcinoma tumor tissue does not show a dependence on the area, intensity and total score of ER and PR, as well as on the HER2 status of the tumor and the proliferative marker Ki67.

12. High nuclear expression of RIPK3 in tumor tissue is associated with low progression-free survival in patients with breast cancer.