**DISSERTATION ABSTRACT**

**„Metabolomics studies of cancers based on model systems and patients samples”**

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The doctoral dissertation consists of four main chapters based on use of metabolomics in the field of cancer research. Mainly focusing on changes in biochemical processes that occurs as a result of disturbed body homeostasis. Biological matrices in form of patients samples and model systems provides information that allows for verification observable biochemical disturbances during the pathological state - cancer. Measured variability in the profile of low-molecular-weight compounds allows for potential intergroup discrimination for diagnostics or disease progression and identification interesting biochemical pathways for further research in drug discovery.

The first chapter of the dissertation focuses on metabolomics studies using 1H NMR spectroscopy for selected thyroid diseases (NN, FA, TC) based on patients serum and urine samples. Early detection of nodules on the thyroid gland, including thyroid cancer, continues to be mainly based on invasive procedures such as fine needle aspiration biopsy. Therefore, there is a need to develop new diagnostic methods that could provide a less invasive, clinically useful method for distinguishing nodular thyroid changes. Hence, the analytical profiles of 1H NMR spectra were collected from paired urine and serum samples from control and patients group. Determination the predictive potential of metabolites for discrimination needs on studied groups was assessed with chemometric methods. Both urine and serum have been shown to contain sufficient information to distinguish patients with nodular changes from the control group. In addition, the use of data fusion from both types of biological materials in single data matrix has allowed for further improvement of models quality, and increased theirs prediction possibilities.

The second chapter analyses haematological cancers with utilization of metabolomics approach. Hematologic malignancies are a frequently diagnosed group of cancers and an important death cause. The effective treatment of these diseases is based on early and accurate detection. Specific low-molecular-weight compounds released by malignant cells and simultaneous reaction of the organism through disturbance in biochemical equilibrium can serve as diagnostic and prognostic biomarkers, and also as a tool to manage cancer therapy. In order to identify the most important metabolites allowing for the differentiation of selected hematological malignancies, the 1H NMR spectroscopy was used. The study was carried out on 116 methanol serum extract samples from AML (n = 38), nHL (n = 26), CLL (n = 21) and HC (n = 31). Multi-dimensional and one‑dimensional data analysis was applied to identify changes in low-molecular-weight compounds in studied groups. The complex and detailed VIP‑PLS‑DA models have been calculated to reveal possible discrimination between studied groups and variability in biochemical pathways. The predictive properties of the chemometric models were confirmed by ROC curves and statistical analysis. Complex models representing the most important changes among studied group allow to select two sets of eight important metabolites in the HC/AML/CLL/nHL and five in the AML/CLL/nHL comparisons.

The third chapter uses serum metabolomics for screening breast cancer. The possibility of a non-invasive screening method in breast cancer appears to be essential to reduce the risk of metastasis. The decision to carry out a biopsy is necessary to establish a diagnosis and to set right approach for treatment. However, biopsy is not a suitable tool for screening due to its invasiveness. Metabolomics with the possibility of high-throughput analyses of biological material could be a alternative to the first stage in clinical diagnostics or empirically supporting and justifying the decision to perform a biopsy. At the same time serum metabolomics, enables for routine control even with basic medical examinations, e.g. morphology. A comprehensive approach to breast cancer using a control group and patients group (invasive ductal carcinoma and ductal carcinoma in-situ) allowed to calculate chemometric models with high sensitivity and specificity indicating high potential of metabolomics in screening. Simultaneously, allowing for discrimination between these two main cancers subgroups - IDC and DCIS. Moreover, enabled also to distinguish control groups from cancer subgroups with specific molecular types: luminal A and luminal B. Additionally, statistical analysis among selected compounds identified biomarkers that may be used for cancer progression between I and II (IA/B and IIA/B) stage.

The final chapter of the doctoral dissertation is based on metabolomics studies of triple negative breast cancer based patients samples and MDA MB-468 cell line. Highlighting differences in the organism response and changes at the cellular level. Breast cancers belong to the of heterogeneous group and among them, there is one particular type - triple negative breast cancer (TNBC). TNBC is characterized by negative results for the progesterone receptor, the estrogen receptor alpha and the HER2 receptor. Differences in the cancer functioning and utilization of specific biochemical pathways may lead to changes in metabolites that are essential for its development. The study used a TNBC patients and control group to verify differences in the profile of serum low-molecular-weight compounds and comparison changes to in MDA-MB-468 cell line footprint. Additionally, to emphasize the importance of particular biochemical pathways in TNBC, a cell culture time event experiment was performed, in which different supplementation conditions (endogenous amino acids, EAA).