DESCRIPTION FOR THE GENERAL PUBLIC

All cells of the human body contain the same genes, but not in all of them all genes are expressed. Gene expression is the process by which information from a gene is used in the synthesis of a functional gene product (protein or RNA). The pattern of gene expression is maintained by a specific epigenetic mechanisms, which involve the change of the expression of specific genes without change in their nucleotide sequence.

One of the basic mechanisms of epigenetic regulation of gene expression is the methylation of cytosine residues in DNA (5-methylcytosine arises). A specific DNA methylation pattern depends not only on the course of the process of attachment of methyl groups to cytosine residues, but is also the result of the process of passive and active DNA demethylation. Recent reports suggest that very important role in DNA demethylation play TET proteins (ten-eleven translocation), the enzymes that catalyze the hydroxylation (adding the hydroxyl group (-OH) to the compound molecule) of 5-methylcytosine to 5-hydroxymethylcytosine. In human, three TET proteins, named TET1, TET2 and TET3, have been identified. In many types of cancers a decreased expression of *TET1* and *TET2* is observed. Reduced amount of TET protein is often associated with development and progression of tumors. However, the results of our preliminary research revealed that TET3 behaves differently from other members of TET family. In advanced tumor stages the gene expression of *TET1* and *TET2* was decreased, while the expression of *TET3* was elevated.

The contribution of TET proteins in the regulation of gene expression is not confined to their enzymatic activity. TET proteins may interact with proteins involved in modification of histones (a small, alkaline proteins, which are components of the chromatin), thus affecting their activity. One of the proteins that interact with TET proteins is an enzyme O-GlcNAc transferase (OGT). OGT catalyzes the attaching of single sugar moieties to proteins, and this process is called O-GlcNAcylation. Escalated expression of the gene encoding OGT, as well as the increased of O-GlcNAcylation levels are hallmarks of many types of cancers. TET proteins can interact with O-GlcNAc transferase, allowing transport of this enzyme to the chromatin, where it modifies the histones. Accordingly, the complex OGT-TET affects the regulation of genes expression. Although all three TET family members can be involved in the recruitment of OGT to the chromatin, it is suggested that a crucial role in this process play TET3. This seems to be confirmed by the results of several tests.

Based on the available data and already conducted own research, we hypothesized that the interplay between TET3 and OGT may have a significant impact on the process of tumor progression. Our goal will be to determine if the interaction between OGT and TET3 affects the regulation of expression of genes associated with the ability of cells to invade and metastasize. The planned study will be carried out using cell lines of endometrial and breast cancer and non-cancer cell lines of mammary gland, and as well as using a clinical samples derived from patients with endometrial cancer. In order to determine how the change of *TET3* expression affects the activity of OGT, planned experiments on cell lines will be carried out in different variants of *TET3* and *OGT* expression. Increased or decreased expression of these genes will be conducted by an appropriate method, using special expression vectors (plasmids). Determination of the effects of altered TET3 expression on expression and localization of OGT and as well as on epigenetic modifications changes will be checked by using the Western Blot method. The effect of altered expression of *TET3/OGT* on the expression of selected genes, whose protein products are involved in the progression of cancer, and as well as on the localization of the OGT in the sequences encoding these genes will be characterized. The global level of 5-methylcytosine and 5-hydroxymethylcytosine, as well as the potential of tumor cells to migration and invasiveness will be carried out using commercially available assays. The last task planned in the project will be to analyze the expression level of *OGT* and selected genes involved in tumor progression in clinical samples of endometrial cancer. We will be looking for a correlation between the expression of *TET3/OGT* and the expression of examined genes. In addition, the results will be analyzed and correlated with clinical and pathomorphological data.

Understanding the mechanisms involved in maintaining the correct formula of epigenetic modifications may be very important for better understanding the process of malignant transformation and thus contribute to the development of new methods of diagnosis and therapy of cancer.