The effect of apelin on colon cancer progression

Colorectal cancer (CRC) is the third most common diagnosed cancer worldwide. Despite the fact, that recently the number of new cases and deaths decreased, the probability of suffering from colorectal cancer is still about 4 – 5%. One of the main cause increasing this probability is obesity. Augmented mass of adipose tissue, which is endocrine organ, leads to intensified secretion of adipokines – bioactive molecules comprising hormones, growth factors, angiogenic factors and cytokines. There are many well-known adipokines, including leptin, adiponectin, and resistin. However, some studies focused on novel adipokine - apelin. It is a secreted peptide and a ligand for G-protein coupled receptor – APJ. It is produced in cell as a prepropeptide, that could be cleaved producing several apelin peptides, e.g.: apelin-36, -17, and -13. The latter could be modified producing a piroglutaminated form of apelin-13. Under normal conditions apelin and its receptor, which together create the apelinergic system, are involved in regulation of many physiological processes, such as body fluid homeostasis, regulation of cardiovascular system or metabolism. Recently, many studies focused on participation of apelin in pathological processes, including heart failure, diabetes, obesity and cancer.

The aim of the doctoral dissertation was to determine the effect of apelin on colon cancer progression. Thereupon, purpose of this project was to examine the influence of this adipokine on processes connected with carcinogenesis, such as migration, invasion and proteolytic activity of the cells.

In the first stage of the project the analysis of the CRC patients' samples was done. The experiments showed that the mRNA and protein level of apelin and its receptor was higher in tumors than in control tissue. Moreover, serum levels of apelin and APJ were also increased in CRC patients in comparison to controls. The concentration of serum apelin level significantly increased in individuals characterized by higher TNM stage, as well as with lymph node and distant metastasis.

Additionally, the influence of four apelin peptides - apelin-36, -17, -13, and [Pyr1]apelin-13, on processes connected with carcinogenesis was also studied. It was shown that peptides increase migration, invasion and proteolytic ability of colon cancer cells. It is probably mediated through PI3K/AKT and MAPK signaling pathways.

Furthermore, the influence of apelin (*APLN*) and APJ receptor (*APLNR*) genes modifications on previously mentioned processes was tested. It was demonstrated, that cells with augmented

level of apelin receptor are characterized by increased ability to migrate and invade. The opposite effect was observed in cells with downregulated level of *APLN*.

In the last stage the effect of tumor microenvironment on colon cancer cells was examined. For this purpose the co-cultures of colon cancer cells and adipocytes or endothelial cells, which secrete apelin, were used. Under these conditions, migration and invasion abilities of colon cancer cells were increased in comparison to control cells.

In conclusion, obtained results indicate significant influence of apelin on colon cancer progression. Stimulation of cancer cells with apelin peptides, as well as genetic modifications showed that this adipokine has an effect of processes connected with carcinogenesis.