Abstract in English

Colorectal cancer is currently one of the three major causes of cancer-related death. In order to help clinicians to treat colorectal cancer, it is necessary to introduce more effective tools that will improve not only early diagnosis, but also prediction of the most likely progression of the disease and response to chemotherapy. This thesis aims to describe the most accepted biomarkers among those proposed for use in CRC divided based on the clinical specimen that is examined (tissue, feces or blood) along with their restrictions. In relation to my research, the thesis will also focus on alternative splicing that has emerged as an important regulator and potential treatment target in CRC. Alterations in gene expression leading to colorectal carcinogenesis results in dysregulated levels of nucleic acids and proteins, which can be utilized for the identification of modern, minimally invasive molecular biomarkers. One of the alternative splicing factors are MBNL proteins. The goal of my work that will be presented here was to analyze gene expression of the MBNL family of regulators of alternative splicing in various stages of colorectal cancer development, together with the MBNL-target splicing events in FOXP1 and EPB41L3 genes and tumor-related CD44 variants.

The study was done using samples of tumor tissue and non-malignant mucosa from 108 CRC patients. After RNA isolation and reverse transcription, the relative gene expression of a selected gene panel was tested by quantitative real-time PCR, followed by statistical analysis. We observed that MBNL expression was decreased in tumor tissue compared to non-tumor mucosa. In addition, lower expression was observed for the variants of FOXP1 and EPB41L3, while higher expression in tumor tissue was detected both for total CD44 and its cancer-related variants 3 and 6. Transcript levels of the MBNL genes were not found to be related to any of the studied clinicopathological characteristics. Multiple significant associations were identified in the target gene panel, including higher transcript levels of FOXP1 and CD44v3 in patients with distant metastases and connections between recurrence-free survival and altered levels of FOXP1 and CD44v3. Our results identified for the first-time deregulation of MBNL genes in colorectal cancer. Given the physiological role of MBNL proteins, we hypothesized that down-regulation of their transcripts in tumor tissue compared to matched non-tumor mucosa can lead to transition of alternative splicing patterns towards a less differentiated phenotype, that induce further tumor development. We believe that our research highlights the importance of alternative splicing regulation for tumor growth and propagation.