Abstract

Colorectal adenomas (CRA) represent precancerous lesions for the development of colorectal cancer (CRC), a disease associated with up to one million deaths worldwide annually. Currently, only two biomarkers (carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9)) are established in clinical and diagnostic practice for detecting the presence of CRC, but none for detecting their precursors. However, early detection of CRC patients is crucial for reducing mortality from this disease.

The aim of this dissertation was to investigate the precancerous stages of CRC and search for markers that would discriminate both the initiation of CRA formation from healthy mucosa and the transition from CRA to adenocarcinoma. To achieve these goals, it was necessary to explore the genetic background of CRA tissue on several levels: I) gene expression of the entire transcriptome isolated from CRA tissue, II) methylation profile of DNA isolated from CRA, III) chromosomal instability of the entire genome of CRA including telomere length and mitochondrial DNA content, and IV) mutation profile of genes associated with tumorigenesis in DNA isolated from CRA.

The main outputs of this dissertation are: I) Based on transcriptome analysis and methylation profiling, six candidate genes (*MMP7*, *MMP1*, *CLDN1*, *CLDN2*, *ETV4*, and *TACSTD2*) indicating the transition from healthy tissue to CRA were proposed, and one of them, *TASCTD2*, also overlapped with incipient CRC stages, II) At the level of chromosomal instability, a significant amplification of the long non-coding RNA (lncRNA) *MALAT1* was found in CRA tissue, which could determine its future development into CRC. This lncRNA was also monitored at the expression level, where *MALAT1* lncRNA levels were elevated in the plasma of patients with CRA and CRC compared to healthy individuals, potentially serving as a promising diagnostic marker, III) Another indicator of CRA development was the observation of telomere shortening in CRA tissue and simultaneously increasing copies of mitochondrial DNA compared to adjacent mucosa, IV) The mutation profile revealed changes in the sequence of genes *APC*, *KRAS*, *TP53*, *FBXW7*, and *PIK3CA*, and their association with the mutation frequency from CRA with low dysplasia to CRA with higher degrees of dysplasia to CRC.

The results of the dissertation provide several new markers of the transition from healthy intestinal tissue to CRA and subsequently to CRC, which could be further expanded by additional independent research to more thoroughly investigate the markers identified by us with the aim of introducing them into clinical practice.