miR-483-3p, miR-483-5p, and miR-514a-3p: NEW PROMISING BIOMARKERS FOR COLORECTAL CANCER

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Introduction: Colorectal cancer (CRC) is globally ranked as the third most incident malignant neoplasm. In Brazil, high mortality rates are observed, with delayed screening and diagnosis contributing to poorer prognoses. In this context, microRNAs (miRNAs) have emerged as promising biomarkers for various diseases. **Objective:** To validate the biomarker potential of differentially expressed miRNAs across different stages of CRC. **Methodology:** This study was conducted in compliance with ethical standards (Declaration of Helsinki and the Nuremberg Code). Approval was granted by the Ethics Committee of the Oncology Research Center at the Federal University of Pará (UFPA), under protocol CAAE: 69029323.0.0000.5634. An in silico analysis was carried out to identify miRNAs differentially expressed in CRC using data from the TCGA (The Cancer Genome Atlas, COAD - Colon Adenocarcinoma, READ - Rectum Adenocarcinoma). Through pre-established filters, a list of miRNAs was obtained. Their interactions with target genes were enriched using the miRWalk web tool, and the resulting gene list was submitted to the OncoKB™ platform to confirm cancer-related genomic annotations. Subsequently, the Reactome and Cytoscape web servers were used to analyze biological pathway alterations and to generate the interaction network. For in silico validation using RT-qPCR, 400 tumor tissue samples from patients diagnosed with CRC and 100 samples from cancer-free patients (screened by colonoscopy) were analyzed at Ophir Loyola Hospital in Belém, PA. Differential expression data and clinical information sex, age groups (30–49; 50–69; 70–99), stages I–IV, and histopathological differentiation were statistically analyzed using R Studio version 4.2.2. The level of statistical significance was set at $p \leq 0.05$, with correction by False Discovery Rate (FDR). **Results:** From the list of most differentially expressed miRNAs, three have already been processed (hsa-miRNA-483-3p, hsa-miRNA-483-5p, and hsa-miRNA-514a-3p). All three miRNAs showed statistically significant differences ($p<0.05$) across cancer stages (I–IV), with respective AUC values of 0.769, 0.489, and 0.546 indicating that the first miRNA has the most potential as a biomarker. A significant difference was also observed in hsa-miR-514a-3p expression concerning cellular differentiation. No significant differences were found related to sex or age groups ($p>0.05$). Collectively, these miRNAs regulate 53 target genes that significantly influence a total of 338 biological pathways, most of which are associated with signal transduction. Among the 11 genes targeted by more than one of the investigated miRNAs, 3 are oncogenes, 3 are tumor suppressors, and 5 have no clinical cancer annotation. Of these, six genes are closely related to key biological pathways in cancer development. **Conclusions:** This study contributed to the validation of miR-483-3p, miR-483-5p, and miR-514a-3p, which play important roles as biomarkers for CRC diagnosis, prognosis, and as potential therapeutic targets. The findings enhance the understanding of miRNA expression in the northern Brazilian population. Furthermore, the miRNA–target gene interaction network helps elucidate the complexity of CRC progression, supporting future research aimed at identifying biomarkers as strategies for treating complex diseases such as cancer.

Keywords: CRC; miRNAs; prognosis.