LncRNA UCA1, Upregulated in CRC Biopsies and Downregulated in Serum Exosomes, Controls mRNA Expression by RNA-RNA Interactions

Long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) contribute to the onset of many neoplasias through RNA-RNA competitive interactions; in addition, they could be secreted by cancer cells into biological fluids, suggesting their potential diagnostic application. By analyzing the expression of 17 lncRNAs and 31 circRNAs in biopsies and serum exosomes from colorectal cancer (CRC) patients through qRT-PCR, we detected CCAT1, CCAT2, HOTAIR, and UCA1 upregulation and CDR1AS, MALAT1, and TUG1 downregulation in biopsies. In serum exosomes, UCA1 was downregulated, while circHIPK3 and TUG1 were upregulated. Combined receiver operating characteristic (ROC) curves of TUG1:UCA1 and circHIPK3:UCA1 showed high values of sensitivity and specificity. Through in vitro (i.e., RNA silencing and mitogen-activated protein kinase [MAPK] inhibition) and in silico analyses (i.e., expression correlation and RNA-RNA-binding prediction), we found that UCA1 could (1) be controlled by MAPKs through CEBPB; (2) sequester miR-135a,miR-143,miR-214, andmiR-1271, protecting ANLN, BIRC5, IPO7, KIF2A, and KIF23 from microRNA (miRNA)- induced degradation; and (3) interact with mRNA 30-UTRs, preventing miRNA binding. UCA1 and its co-regulated antisense LINC01764 could interact and reciprocally mask their own miRNA-binding sites. Functional enrichment analysis of the RNA-RNA network controlled by UCA1 suggested its potential involvement in cellular migration. The UCA1 regulatory axis would represent a promising target to develop innovative RNA-based therapeutics against CRC.

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