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P53-induced miR-30e acts as a tumor and metastasis suppressor miRNA in colorectal cancer

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The tumor suppressor p53 is one of the most commonly altered genes in CRC and it also regulates the expression of several protein and non-protein coding genes. Indeed, a small group of microRNAs have come to be recognized as essential mediators of p53 function. With a genome-wide systematic approach, in this study, we investigated a potential function of p53 in regulating miRNAs that mediate human CRC progression. Therefore, a miRNA microarray was performed on human isogenic CRC cell line pairs (p53 wt and ko) to identify deregulated miRNAs attributable to p53 loss. The analysis revealed members of the miR-30 family, miR-30e particularly, as the most significantly downregulated group in the p53 knock-out cells compared to the wild type. To elucidate the impact of p53 loss on the expression of miR-30e, we also performed p53 overexpression and silencing in CRC cells harboring wt p53. Indeed, p53 silencing resulted in a reduction of miR-30e expression, whereas an increase of mature miR-30e was observed in CRC cells treated with Nutlin-3a, a specific MDM2 antagonist known to increase p53 expression or activity. Furthermore, we identified miR-30e to be a direct novel transcriptional target of p53.

Additionally, gain and loss of function experiments revealed miR-30e to be a significant negative regulator of tumor cell migration, invasion and *in vivo* metastasis mediated by integrins alpha-6 (ITGA6) and beta-1 (ITGB1) as novel targets of the miR-30e. This miRNA also significantly reduced tumor cell proliferation in part by causing G1/S cell cycle arrest, which was achieved by inducing p21 and p27 expression. Finally, we found miR-30e to be lost in resected colorectal cancer tumors as compared to normal colon tissues of human patients. Taken together, miR-30e is an important tumor suppressor miRNA able to activate the expression of cell-cycle checkpoint inhibitors, and it is a novel effector of p53-induced suppression of migration, invasion and metastasis.