

MIR-137-MEDIATED LOSS OF KDM5B EXPRESSION LEADS TO SUPPRESSION OF THE MALIGNANT PHENOTYPE OF BLADDER CANCER CELLS

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The oncogenic role of KDM5B is implicated in the pathogenesis of many cancers including bladder cancer (BC). KDM5B is a histone demethylase enzyme that modifies the chromatin structure to specify cellular transcriptional states. Overexpression of KDM5B in cancer cells is correlated with an increased proliferative capacity. Intriguingly, KDM5B is a cancer/testis antigen; while its expression in tumours is ectopically amplified, KDM5B expression in normal conditions is limited to embryonic stem cells (ESCs) and the testis in adults. These unique characteristics make KDM5B a potential pan-cancer therapeutic target. Thus, this study was aimed at identifying potential regulators of KDM5B. Since KDM5B expression in ESCs is orchestrated by microRNAs (miRNAs) and the expression of many miRNAs are altered in BC, we hypothesized that miRNAs may be the switch that can abate KDM5B expression to mitigate the BC malignant phenotype. Based on IHC- and RT-QPCR analysis, we found that KDM5B protein and transcript levels were differentially expressed in cancer tissues and cell lines, respectively. Amongst several *in silico*-predicted putative KDM5B-targeting miRNAs, the *in vitro* basal expression of miR-137 was inversely correlated with KDM5B expression. We demonstrated that the overexpression of miR-137 significantly attenuated KDM5B expression, induced G1 cell-cycle arrest, suppressed cell growth and blocked invasion and migration of BC cells. In contrast, downregulation of miR-137 expression led to the reverse effect. By integrating *in silico* screens of miR-137 putative target genes and microarray data using the Ingenuity Pathway Analysis (IPA), we revealed that miR-137 possibly exerts control over the cell-cycle through Rb and adenylyl cyclic signalling pathways by targeting key regulators of cyclin A. We also showed that miR-137 gain-of-function increased the expression of tumor suppressor, JDP2. While our results suggest that miR-137 can mitigate the KDM5B-associated BC phenotype, further studies on understanding the effect on aberrant histone methylation patterns are warranted.