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Transcriptional Repressor Kaiso Promotes Epithelial to Mesenchymal Transition and Metastasis in Prostate Cancer through Direct Regulation of miR-200c

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ABSTRACT

The loss of miR-200 family, through DNA methylation, results in cancer cells undergoing an epithelial to mesenchymal transition (EMT), and metastasis. In this study, we established that the transcriptional repressor Kaiso directly binds methylated regions of the miR-200 family, and this is reversed with 5-aza treatment. sh-Kaiso PC-3 cells display increased miR-200-a/b/c, miR-141, and miR-429 expression, with miR-200c demonstrating the most significant increase. Interestingly, overexpression of EGFR or treatment with EGF decreases miR-200c expression and this is reversed after treatment with EGFR specific kinase inhibitor PD153035. However, EGF did not have a significant effect on miR-200c in sh-Kaiso DU-145 or PC-3 cell lines, suggesting Kaiso silences miR-200c through the activation of EGFR signaling. Overexpression of Kaiso in LNCaP cells results in decreased expression of miR-200-a/b/c, miR-141, and miR-429, along with increased expression of ZEB1, p-EGFR and total EGFR levels. Overexpression of miR200c in PC-3 cells results in decreased expression of EGFR, ZEB1, ERK1/2 and Kaiso. Additionally, sh-Kaiso PC-3 demonstrates reduced *in vivo* tumor formation and metastasis. Thus, our data suggests that EGFR signaling regulates the silencing of miR-200 family through Kaiso binding to methylated regions in the promoter.