Mesenchymal compartmentalization of miR-1 and miR-143 in prostate tissue and loss of expression in tumor-associated stroma

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Background: Mesenchymal-specific genes can be misinterpreted as potential tumor suppressors when relatively lower transcript levels are detected in carcinomas, as was recently discovered for miR-143/145. In light of this, we examined the epithelial and mesenchymal nature of several putative tumor suppressive and oncogenic miRNAs in human prostate cancer (PCa).

Methods: We applied Expression Microdissection (xMD) and Laser Capture Microdissection (LCM) to isolate stromal and epithelial tissue from radical prostatectomy specimens. Individual miRNAs were quantified by droplet-digital RT-PCR. Bioinformatic analyses determined the correlation of miRNAs with stromal marker expression and clinical outcomes. Human prostate stromal cultures were developed and transfected with miRNA mimics/inhibitors or treated with receptor tyrosine kinase (RTK) inhibitors or ligands. Cell migration was investigated by persistence migratory directionality assay.

Results: Strikingly, the expression of miR-1 and miR-143 was predominantly mesenchymal. Conversely, miR-141 was almost exclusively epithelial. The levels of miR-1 and miR-143 were significantly lower in tumor-associated prostate stroma than in normal prostate stroma. Also, stromal marker expression directly correlated with miR-1 and miR-143 in the TCGA-PRAD, while miR-141 was inversely correlated. Reduced miR-1 and elevated miR-21 were associated with biochemical recurrence. In stromal cultures, miR-143 was stimulated by RTK inhibitors and suppressed by their ligands. Inhibition of miR-143 attenuated stromal cell migration.

Conclusions: We demonstrate that miR-1 and miR-143 are predominantly stromal miRNAs, thus challenging their roles as prostate cancer tumor suppressors. We further reveal that the levels of miR-1 and miR-143 are diminished in tumor associated stroma, implicating a new role for these miRNAs in the tumor microenvironment. We further show that reduced miR-1 and elevated miR-21 are associated with biochemical recurrence, and that miR-21 levels are associated on top and beyond Gleason grade and stage in multivariate analysis. This data suggests that miRNAs in tumor associated stroma may provide prognostic information for PCa and miRNA-targeted therapy must consider cell-type specificity of miRNA expression.

Conflict of Interest: The authors have no relevant conflicts to disclose

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