Editorial Commentary

New functions assigned to a microRNA with genetic links to prostate cancer risk

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Germline genetic analyses have begun to identify links between microRNA (miRNA) binding sites and the heritable risk of developing prostate cancer (PCa). Interestingly, one of the most significant links involves the diagnostic biomarker, PSA. This discovery was first reported in 2015, from a large genome-wide association study (GWAS) of samples from 23 different studies participating in the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) Consortium (1). The single-nucleotide polymorphism (SNP), rs1058205, is located in the 3'-untranslated region (3'-UTR) of the gene that encodes PSA, KLK3 (2). Previous studies have found associations between the rs1058205 SNP and serum concentrations of PSA (3,4). The rs1058205 T-allele creates a new binding site for the mature miRNA, miR-3162-5p. When LNCaP PCa cells, which are homozygous for the rs1058205 T-allele, are transfected with miR-3162-5p mimics, the levels of PSA mRNA and protein are decreased (1). This year, a follow-up study from the Australian Prostate Cancer Research Centre-Queensland (APCRC-Q) sheds new light on the expression and activity of this PCa associated miRNA.

The new study, published in Clinical Chemistry, validates the ability of miR-3162-5p mimics to inhibit PSA mRNA and protein expression in LNCaP PCa cells (5). The cultured media of transfected cells correspondingly contained lower levels of free and total PSA. Remarkably, additional members of the kallikrein family (KLK2 and KLK4), and the Androgen Receptor (AR), were found to be targeted and suppressed by miR-3162-5p. RNA pull-down studies demonstrated direct interaction between biotinylated miR-3162-5p duplexes and KLK2, KLK3, KLK4, and AR mRNA. These new results suggest that miR-3162-5p may regulate specific kallikrein gene family members directly, through miRNA directed RNA interference, and indirectly, through AR suppression. These discoveries add miR-3162-5p to a list of other miRNAs reported to target and suppress AR and/or PSA in PCa cells (6-13). Proteomic experiments uncovered additional metabolic pathways affected by miR-3162-5p mimic transfection, including oxidative phosphorylation, fatty acid metabolism, adipogenesis, and glycolysis (5).

The current manuscript also reveals that miR-3162-5p induces a tumor-suppressive phenotype in PCa cells (5). Androgen-sensitive and AR-positive LNCaP cells showed diminished proliferation and colony formation approximately 72 hours after miRNA mimic transfection, consistent with the time required for typical miRNA-mediated gene silencing. This anti-proliferative effect was not observed in AR-negative and PSA-negative PC3 PCa cells. However, miR-3162-5p strongly suppressed colony formation in PC3 cells. Therefore, this miRNA may affect cells differently, depending on cell state and available mRNA targets.

The manuscript also provided new results on the expression of miR-3162-5p in human prostate tissues (5). Quantitative RT-PCR analyses did not detect statistically significant differences in miR-3162-5p levels between

normal (N=12) and PCa (N=42) tissues. Although, a subset of PCa specimens had relatively higher levels of the miRNA. The study did find that more aggressive (higher Gleason grade) tumors exhibited significantly higher average levels of miR-3162-5p. These results suggest that miR-3162-5p levels may be informative, as a prognostic tissue biomarker, to distinguish high-risk from low-risk PCa.

The elevated level of miR-3162-5p in aggressive PCa tissue is somewhat perplexing, when considering the tumor-suppressive nature of the miRNA mimics in PCa cell lines. It is possible that other cell types, within the prostate tumor microenvironment, also express miR-3162-5p and contribute to the elevated levels detected in aggressive disease. Recent studies have found that miRNAs from cancer-associated stroma are readily detectable in macrodissected solid tumor tissue, and that overall miRNA levels in tissue may not always be representative of miRNA expression in cancer cells (14,15). At the same time, miR-3162-5p may induce different phenotypes *in situ* versus in cell culture. Further studies are required to resolve this apparent discrepancy in expression level and tumor-suppressive activity.

In conclusion, miR-3162-5p is a miRNA of continued interest for PCa due to its elevated detection in higher-grade disease, its association with the PCa risk SNP, rs1058205, and its ability to inhibit PCa cell proliferation and colony formation. Ongoing studies are required to define the cell-type-specific expression of miR-3162-5p in normal prostate and PCa tissue, and to validate its association with higher risk disease. Future studies are also required to define the MIR3162 gene locus, its primary transcripts, and the upstream pathways that regulate expression. Finally, miR-3162-5p inhibition, or gene knockout, will be important to validate mRNA targets and to determine the endogenous activity of this cancer-associated miRNA, particularly with respect to the rs1058205 SNP and PSA expression, as well as tumor growth.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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