Commentary

Is microRNA expression profile in prostate cancer dependent on clinicopathologic stage or cell subtype?

Karthik V. Giridhar[1], Manish Kohli[1], Liang Wang[2]

[1]Department of Oncology, Mayo Clinic, Rochester, MN, USA; [2]Department of Pathology and MCW Cancer Center, Medical College of Wisconsin, Milwaukee, WI, USA

Correspondence to: Liang Wang, MD, PhD. Department of Pathology and MCW Cancer Center, Medical College of Wisconsin, Milwaukee, WI 53226, USA. Email: liwang@mcw.edu.

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The identification of reliable prognostic and predictive biomarkers for monitoring prostate cancer remains an important research goal. Ideally, such biomarkers will transform clinical decision-making by providing clues to each individual patient's disease aggressiveness, response to therapy, and risk of recurrence. Genomic approaches in early stage localized prostate cancer have been used for predicting treatment outcomes. One example of this type of genomic test is the Mi-Prostate Score (MiPS), which incorporates blood PSA levels and urinary levels of *TMPRSS2-ERG* and PCA3. Other examples include the Oncotype DX prostate cancer test (a tissue-based multi-gene expression assay that predicts outcomes after localized stage treatments), the ConfirmMDx (DNA methylation profiling used to diagnose prostate cancer), and the Prolaris test (prognostication in localized stage disease based on cell cycle progression genes) (1). These tests are specifically applied in localized stages based on the premise that evolution of subclones of malignant cells is dependent on stage and pathology. Novel tests being evaluated include small non-coding RNAs (in particular, microRNA, or miRNA), protein-coding genes (mRNA) and their abundant levels in circulating microvesicles or exosomes. However, all these tests are based on clinical stage and pathology.

miRNAs are small non-coding RNAs involved in regulating gene expression via inhibiting target mRNAs (2). A growing field of literature indicates that miRNAs can function either as oncogenes or tumor suppressors and hold the promise of being used clinically as biomarkers. Dysregulation of miRNAs has been implicated in cancer proliferation, differentiation, apoptosis and metastases (3). miRNA signatures are also attractive from a clinical standpoint because they can be obtained and detected in a wide variety of clinically available samples including tumor tissues, sera, plasma, and urine.

Validation of miRNA-based signature, however, has been a challenge. While many studies have described miRNA expression profiles in prostate cancer, the results have been difficult to validate across studies. In a review conducted by Bertoli *et al.*, 16 studies identified 44 intracellular miRNAs with prognostic value, however only 6 were identified in more than one profile (4). One possible explanation for the inconsistent results would be that cancer-specific changes in miRNA expression may be cell-type specific (5), and none of the previous studies have fractionated miRNA expression by cell subtype. If this were the case, robust and significant differences in expression profiles may exist across samples, though relatively small and washed out in samples with heterogeneous cell types.

In this study published in *European Urology*, Rane *et al.* investigated this hypothesis by examining miRNA expression in tumor specimens presorted by cell type (6). This study evaluated samples from patients with benign prostatic hyperplasia, treatment-naïve prostate cancer, and castration-resistant prostate cancer. This study then performed genome-wide miRNA expression analysis on three cell types found in the prostate epithelium: stem-like cells (CSCs), transit-amplifying cells, and committed

basal cells. By comparison of the unique miRNA expression profile from each sample, principal component analysis showed a closer clustering of signatures related to cell type, not pathologic status. Further, their results suggest that the differentiation stage of a prostate epithelial cell is the primary influence on its miRNA profile.

So how can we find a miRNA signature that tells us something about disease state? To address this question, Rane *et al*. focused on miRNAs in prostate cancer CSCs, which make up a small population of tumor cells. Accumulating evidence indicates CSCs play a role in tumor initiation, progression, relapse, metastases, and therapy resistance (7). By separating cell subtype initially, this study identified numerous novel and cell subtype specific miRNA candidates, with miR-548c-3p being a key regulator in maintaining stem cell like properties, including increased colony-forming efficiency, increased expression of stem cell proteins, and acquired resistance to radiation.

The results from Rane *et al*. (6) provides solid evidence supporting that cell subtype-specific miRNA expression differences are one of the reasons behind previously observed heterogeneous miRNA expression profiles in unfractionated prostate tumors. This study, however, used short cell culture to enrich target cells. Since the cell culture significantly affects gene expression profile, primary cells sorted directly from surgical specimens would be a more valid option. A particular challenge for this type of approach, however, is the considerably additional expertise required to separate a tumor specimen into different cellular subtypes (8). Additionally, researchers have identified multiple additional populations consistent with prostate CSCs (9), adding another layer of complexity to identifying cell subtype.

This study also raises an interesting question: do CSCs share similar miRNA expression patterns across different cancer types? If they do, can we treat cancer patients by targeting these shared miRNA molecules? In addition to cell type and pathological status, inconsistent results may be related to technical limitation such as miRNA quantification without considering isomiRs (miRNA variants, which are commonly seen in RNA sequencing data). Nevertheless, Rane *et al*.'s study clearly demonstrates that cell type-specific and differentiation-specific differences contribute to the significant variations in published cancer miRNA profiles.

We have access to incredible quantities of diverse data types, yet identifying robust and reproducible prognostic biomarkers remains elusive. Rane *et al*.'s study highlights a novel approach to identifying miRNA signature by focus on cell subpopulation, which yields two unique advantages. First, we are able to limit the scope of analysis to relevant changes in tumor biology opposed to other changes in adjacent stromal tissue. This may be particularly advantageous for prostate cancer given the relatively small size of the tumor and interrelationship with stroma (10). Second, we are able to target a specific population of cells for therapeutic applications. With single cell technology advances (11), this option has become a reality. By distinguishing expression profiles between CSCs and other cell types, we may identify novel and clinically relevant miRNA-based candidates that drive the progression of cancer.

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Footnote

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