miRNAs as drivers of TMPRSS2-ERG negative prostate tumors in African American men

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1. ABSTRACT

African Americans (AAs) who have PCa typically have more aggressive disease and make up a disproportionate number of the disease deaths, relative to European Americans (EAs). TMPRSS2 translocations, a common event in EA patients, are exploited in diagnostic and prognostic settings, whereas they are diminished in frequency in AA men. Thus, these patients with TMPRSS2 fusion-negative disease represent an under-investigated patient group. We propose that epigenetic events are a significant and alternative driver of aggressive disease in fusion-negative PCa. To reveal epigenetically governed microRNAs (miRNAs) that are enriched in fusion-negative disease and associated with aggressive in AA PCa, we leveraged both our experimental evidence and publically available data. These analyses identified 18 miRNAs that are differentially altered in fusion-negative disease, associated with DNA CpG methylation, and implicated in aggressive and AA PCas. Understanding the relationships between miRNA expression, upstream epigenetic regulation by DNA methylation, and downstream regulation of mRNA targets in fusion negative disease is imperative to understanding the biological basis of the racial health disparity in PCa.

2. GENETIC AND EPGENETIC DRIVERS OF PROSTATE CANCER (PCa) ARE INTEGRATED

Amongst men in the US, PCa is most common non-cutaneous cancer diagnosed and second leading cause of death (1, 2). This cancer is heterogeneous in terms of progression rates, and various genetic and epigenetic alterations are prevalent and appear to be factors in the tumorigenesis and progression of PCa.

Currently, in PCa, the clinical parameters do not accurately predict progression risks to more aggressive stages of disease. For example, the parameters used for assigning men to radical prostatectomy (PSA level, TNM stage and Gleason score) lack the specificity and sensitivity to distinguish accurately men who both need and will be cured by this treatment, from those who will experience treatment failure typified with rising PSA following surgery (so-called biochemical failure) (3, 4). This is of clinical significance, as patients who experience treatment failure are more likely to progress to more aggressive forms of PCa with increased risks of tumor-related mortality (5, 6). Furthermore, compounding these uncertainties are issues concerning the sensitivity and specificity of the PSA test itself (4). The result of this ambiguity is that men who do not require therapy are treated with either radical surgery or high-dose radiation because their physicians are unable to tell who “needs” therapy (1, 2). Thus, identifying and characterizing non-invasive biomarkers to identify those men who need more aggressive treatment are required.

This ambiguity is further obscured because the incidence and natural history of PCas varies between races. American men of African ancestry have a 19%
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higher incidence and 37% higher mortality from PCa compared to men of European ancestry (reviewed in (7-10)). Thus, in African American (AA) PCa patients, the disease appears more aggressive and occurs at a younger age, than in European American (EA) patients.

In an effort to define the disease, multiple groups, including the Cancer Genome Atlas (TCGA) consortium, have added to previous understanding (11, 12) and have established roles for common genetic alterations in PCa (13-15) and novel somatic mutations, including Mediator of RNA Polymerase II Transcription, Subunit 12 (MED12), Forkhead Box A1 (FOXA1), and Speckle-Type POZ Protein (SPOP). The E3 ubiquitin ligase adaptor, SPOP, shows recurrent mutations in 6-15% of tumors across multiple independent cohorts (14, 16). Also supporting the importance of androgen receptor (AR) signaling in PCa and the cross-talk with epigenetic events, the coactivator Nuclear Receptor Coactivator 2 (NCOA2) is commonly amplified (15, 17). Furthermore, mapping of copy number variations re-enforces the significance of PTEN loss and MYC gain (18). Recently, genetic changes have been used to map clonal evolution of metastatic PCa tumors and have revealed the possibility of multi-cancer clonal evolution within a single tumor (19, 20).

The complex nature of cancer phenotypes, however, cannot be explained by genetic components alone (21). Epigenomic modifications and events contribute to cell transformation. These events can be defined as heritable changes to the expression and regulation of gene expression that are not associated with alteration in the DNA sequences (22), although of course deregulated epigenetic events are often downstream of genetic changes (23, 24).

Epigenetic events include the control of chromatin structure and the function of non-coding RNAs, including microRNA (miRNA). Chromatin structure, which is dynamically regulated and generates a highly plastic interface between transcription factors and the genome, governs gene expression. Similarly, non-coding RNA species affect both chromatin structure and transcriptional responses and regulate transcriptional networks. Therefore, these events impact many aspects of cell signaling and function (reviewed in (25)). In turn, chromatin structure is regulated by hundreds of proteins, often acting in large complexes, that initiate local and large-scale control of the position of nucleosomes and the post-translational modifications to the histones contained within nucleosomes (26-29) (reviewed in (30)). These actions also integrate with other complexes that govern the status of DNA CpG methylation. In this manner, the epigenome regulates the transcriptional control of gene networks related to cell proliferation, differentiation, and programmed death.

Epigenomic events appear to play distinct yet complementary roles to genomic events and add to an explanation for the basis of cancer, for many cancers show gene-specific and global changes in DNA CpG methylation and/or altered histone modification patterns (30-34). For example, up-regulation of the histone methyltransferase, Enhancer of Zeste Homolog 2 (EZH2), appears commonly in both localized and metastatic PCas and associates with a poorer prognosis (35, 36). These histone modifications govern tissue-specific gene regulation and are often intertwined with the actions of DNA methyltransferases (DNMTs) (37) to bring about stable and heritable changes in the capacity (both positive and negative) for regulation of gene expression.

3. MICRNORNA ACT AS EPIGENETIC DRIVERS OF PCa

In parallel to the well-established understanding on the role of classical epigenetic events, the role of non-coding RNA in epigenetic regulation of gene expression has also emerged. The four types of small RNAs, namely, small nuclear (sn)RNAs, small nucleolar (sno)RNAs, miRNAs, and transfer (t)RNAs, correspond to as much as 85% of total small annotated RNAs as determined by GENCODE. Similarly, ENCODE data reveals the wide range expression of miRNAs in different normal and cancer cell lines (38), supporting the concept that miRNAs are components of gene regulation networks and are expressed differentially in disease stages. Although miRNAs represent only ~1% of the genome, they are estimated to target 30% of the genes (39). Furthermore, there is de-regulation of miRNAs for a variety of solid tumors, including breast cancers, colon cancers, and PCas (40-44).

In PCa, several miRNAs are differentially regulated and act as both tumor suppressors and onco-miRs. For instance, miR-221 and miR-222 are upregulated in castration-resistant PCa cells (45) and appear to control cyclin-dependent kinase (Cdk) inhibitors p27kip1 and p57kip2, and thus the cell cycle (46, 47), PI3K and PTEN signaling (48), and a range of other signaling events (49-53), although some contradictory findings suggest that the subtleties of miRNA function are not yet fully revealed (54).

Similarly, miR-125b and miR-143 are upregulated in serum samples from patients with metastatic PCa as compared to those from normal individuals (55). Expression of miR-125b in serum of PCa patients is reported to be upregulated as compared to normal controls (56); other studies report it to be downregulated in PCa as compared to normal or benign prostatic hyperplastic samples (57-59). miR-125b regulates cell proliferation in PCa cell lines (60), and is suggested to be upregulated by androgen signaling (61). Functionally, in PCa, miR-125b targets BAK1 (61).
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(a pro-apoptotic member of the BCL-2 gene family) and Eif4Ebp1 (Eukaryotic translation initiation factor 4E-binding protein 1), a gene that encodes a member of a family of translation repressor proteins (58).

Other miRNAs have been identified as tumor suppressors, including miR-143, miR-145, and the miR-200 family. Expression of miR-143 and miR-145 are suppressed in PCAs and negatively associate with metastasis (62). These miRs contribute to PCa progression though the epithelial-mesenchymal transition (EMT) (62) and loss of their repressive effect on the EGFR/RAS/MAPK pathway (62). miR-205 and miR-200 family miRNAs, also downregulated in PCAs, regulate the EMT by targeting ZEB1 and ZEB2 in PCas (50, 63, 64).

4. EXPLOITING SERUM EXPRESSION OF miRNA TO PREDICT PCa

Understanding and exploiting serum miRNA classifiers in PCa patients offers an alternative route to accurate diagnosis of disease. Mandel and Metais first identified serum-borne nucleic acids in 1948; of these, miRNAs potentially hold the greatest diagnostic promise (reviewed in (65)). miRNAs appear to contribute to multiple oncogenic actions in PCas (reviewed in (58)). They are secreted into serum, where they remain stable (66-69) and can be reliably extracted and measured (56, 70-72). Using serum-borne molecules as prognostic markers is attractive for several reasons. First, they can overcome the limitations of inaccurate sampling of the prostate gland for the presence of cancer. Second, they can encapsulate the effects of heterotypic cell interactions within the tumor micro-environment. Third, they can be used as a non-invasive test procedure and, therefore, hold considerable promise to be exploited as accurate and functional prognostic markers of PCa. Reflecting this potential, studies have now established that miRNA expression can identify PCa that is at an advanced stage and distinguish it from less aggressive or indolent states, and tumors that have the potential to become invasive from non-invasive, organ-confined tumors (56-58, 73-77).

Expression of miRNAs is frequently disrupted in malignancies (reviewed in (42)), and epigenetic inactivation via promoter CpG island hypermethylation is commonly observed for miRNAs with putative growth-inhibitory functions (reviewed in (78)). For example, in PCa, promoter hypermethylation is associated with loss of miR-200 family members that regulate the EMT and cell migration/invasion. Similarly, hypermethylation of the promoter of miR-34a prevents its regulation by p53 and thereby distorts apoptosis and other functions (79-82). However, to date, most studies have focused on DNA methylation and miRNA interactions in general without asking if these alterations differ in either specific subgroups or racial populations.

These functional relationships and mechanisms of disruption suggest that miRNAs can be exploited to reveal the basis for fusion-negative PCas. Furthermore, miRNAs hold considerable promise to be exploited as accurate and functional prognostic serum markers of PCa (83-87) because they can encapsulate events within the tumor micro-environment and overcome the limitations of inaccurate tumor sampling at biopsy. From a biostatistical perspective, given that there are fewer miRNAs than mRNAs, genome-wide coverage is more readily achieved, and the statistical penalties typically associated with mRNA genome-wide testing can be avoided (88).

5. TRANSLOCATIONS OF THE TMPRSS2 GENE ASSOCIATE WITH AGGRESSIVE DISEASE BUT DIFFER IN THEIR INCIDENCE ACROSS RACES

To identify men with aggressive cancer, Chinnaiyan and colleagues pioneered approaches for identifying and exploiting translocations across the genome in PCa (89-94). This group identified common, and unsuspected, translocations of the TMPRSS2 gene and the ETS-Related Gene (ERG), which is part of the ETS transcription factor family that has oncogenic functions. The TMPRSS2 gene codes for an androgen-responsive protease specific to prostate cells, whose expression and genetic variation is associated with aggressive PCa (95, 96). Therefore, this fusion leads to overexpression of ERG, which in turn regulates multiple genes, including AR-responsive genes (91) (reviewed (97)). Following this discovery (94), and as a result of these pivotal studies, much attention has been given to the TMPRSS2–ERG and related ETS family translocations as potential biomarkers, with over 600 publications following. These gene translocations are common and are related to disease stage and progression risks (98-101). There is therefore good evidence that they act as an androgen-activated tumor driver, justifying clinical exploitation; however, the biological and clinical significance of this event remains an active research area (102-108). As a result, there have been efforts to exploit detection of these translocation products in urine. The goal of these studies has been to generate a clinically approved, urine-based approach to aid in early detection, in the so-called Mi-Prostate Score (89).

This clinical development depends on frequency of the translocation products in the patient population. The TMPRSS2–ERG translocation (94) is commonly and consistently identified in approximately 50% of EAs. This focus has to some extent overlooked the fact that the prevalence of these fusion products is lower for other ethnicities including AA, Japanese, and Chinese patients (109). The rate of TMPRSS2–ERG translocations in AA men appears to be significantly lower, in the range of 10-30% (110-113). AA patients, in addition to having
lower incidence of TMPRSS2:ERG fusion, also have lower expression of ERG protein (109, 114, 115). For example, in matched cohorts of 91 AA and 91 EA men, there was lower expression of ERG in AA vs EA index tumors (29% vs 63%) (116). This was more pronounced for higher-grade cancers, in which nearly 60% of EA patients were ERG-positive, whereas only 10% of AA patients were ERG-positive (117, 118). Reflecting this discrepancy, the Mi-Prostate Score test is more accurate for EA than AA patients (119). A follow-up publication to these findings found that, in 154 AA men compared to 243 EA men, AA men are more likely to be negative for many common translocations including: ERG-negative, ETS-negative, SPINK1-negative disease (51% v 35%; p=0.02) (5, 120). The absence of these translocations correlated with the AA PCa disease. Thus, while the TMPRSS:ERG fusion may help to diagnose PCa in EA patients, its low frequency in AA patients suggests that it neither helps to explain disease etiology nor aid with accurate diagnosis of aggressive disease in this group. In fact, this presents a problem for all patients who are fusion-negative, but it is particularly devastating for men of African ancestry.

Thus, dissecting the biological basis for TMPRSS2:ERG fusion-negative PCa represents an underexplored and clinically significant need for AA patients and has the potential to be exploited to define new diagnosis and treatment options. To meet this need, we have explored the role of miRNA-mediated mechanisms that drive disease in TMPRSS2 fusion-negative PCas. The rationale was that miRNAs act as alternative epigenetic drivers of PCa and allow precise stratification of patients. The goal was to develop a biological understanding of tumor drivers in AA men.

6. ARE miRNA RACE-SPECIFIC, EPIGENETIC DRIVERS FOR TMPRSS2 FUSION-NEGATIVE PCAs?

Across and within races, the biological basis for TMPRSS2 fusion-negative tumors remains unexplored. Our recent findings and the work of others, however, suggests that epigenetic drivers are consequential in this form of PCa. There are racial differences in the methylome of AA and EA PCa patients (121-124). For example, AR, RARβ2, and other genes have higher methylation prevalence in tumors of AA patients, whereas TIMP3 has higher methylation in non-involved normal AA prostate tissues (125). DNA methylation has also emerged as a regulator of expression for various miRNAs in the progression in PCa (126-128), but the extent of differential CpG methylation in AA and EA PCa remains under-explored.

There are global differences in the pattern of CpG DNA methylation in benign, cancerous, and metastatic samples in fusion-positive vs fusion-negative PCas (129). Similarly, in a larger cohort, methylated DNA immunoprecipitation sequencing identified differential CpG methylation based on the TMPRSS2–ERG rearrangement status (130). These data suggest that DNA methylation events distort gene expression patterns in fusion-negative PCas and drive this disease. Although these events are significant across the genome, we have pursued the relationships between DNA methylation and miRNA expression for strategic reasons.

Together, these data support the concept that altered methylation of miRNA provides an alternative route for the initiation and progression of PCa in AA patients, whose tumors are commonly TMPSS2 fusion-negative. This raises the possibility that racially specific hypermethylation of key miRNAs drives alternative routes for the initiation and progression of PCa in AA patients, independent of TMPRSS2:ERG fusion.

7. AN ANALYTICAL PIPELINE TO EXAMINE CHANGES IN miRNA IN TMPRSS2 FUSION-NEGATIVE PCa

To test this broad goal, we developed an integrative genomic pipeline to identify miRNAs that are associated with altered DNA methylation and TMPRSS2 fusion-negative PCas. We subsequently integrated our previous findings on miRNAs that are predictive of aggressive tumors and AA PCas (86, 87) and combined these findings (17, 131, 132) to identify, in fusion-negative PCa, which of these miRNAs is altered through DNA methylation (Figure 1).

Specifically, we performed analyses of differential expression of miRNA genes (DEG) in publically available data by mining two different PCa cohorts in TCGA: the main TCGA cohort of localized PCa (15) and the Memorial Sloan Kettering Cancer Center (MSKCC) cohort of 91 tumors (17). In the main cohort, we identified 48 miRNA DEG in altered fusion-negative vs -positive disease (p_{corrected} < 0.05) that also associated with reciprocal and CpG DNA methylation (p_{corrected} < 0.05).

In the MSKCC cohort, we identified miRNA DEG in fusion-negative vs -positive disease in smaller numbers of AA and EA patients. To this, we also combined miRNA expression associated with race. Huang et al. (133) evaluated differences in population-level expression in 757 miRNAs in HapMap lymphoblastoid cell lines derived from 53 CEU (Utah residents with northern and western European ancestry) and 54 YRI (Yoruba people from Ibadan, Nigeria). Of all miRNAs evaluated, and after stringent correction for multiple testing, 33 differed between these two ethnic groups, p_{corrected} < 0.05.

Finally, these miRNAs were filtered further to focus on miRNAs that we had established to be associated with disease progression, and with AA
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PCa PCs identified in patient samples and cell lines from Roswell Park Cancer Institute (RPCI) (86) and Tuskegee University (TU) (87). This approach identified 18 miRNAs as associated with aggressive PCa. These are candidates to drive alternative progression pathways in fusion-negative PCa in AA and EA patients. Across these miRNAs, there was an inverse correlation between CpG methylation and expression of associated TMPRSS2 fusion-negative disease, thus providing proof-of-concept that the race-specific miRNAs are differentially expressed in TMPRSS2:ERG-negative tumors (Figure 2). Some of these miRNAs (e.g. miR-125b) have been investigated extensively in prostate tissue, whereas others have few, if any, publications related to PCa (Table 1). For example, miR-376b, which was initially identified from the TU cohort and verified in the YRI cohort to be ancestry-related, has a loss of methylated CpG islands in the promoter region in TMPRSS2:ERG-negative tumors compared to TMPRSS2:ERG-positive tumors; this pattern is seen for many of the miRNAs. miR-376b is associated with the mTOR-related autophagy proteins, TG4C and BECN1, and relates to angiogenesis through regulation of the HIF1alpha VEGFA/Notch1 signaling pathway (134, 135).

8. DOWNSTREAM TARGETS OF KEY miRNA

For several of these miRNAs, we have also characterized known targets and suggest that there is convergence on regulators of the epigenome. For example, miR-125b targets Nuclear Receptor Corepressor 2/Silencing Mediator Of Retinoic Acid and Thyroid Hormone Receptor (NCOR2/SMRT) (136) and an interacting co-factor that governs CpG methylation dependent silencing, Zinc Finger And BTB Domain Containing 33 (ZBTB33/Kaiso), which targets miR-125a-5p, a member of the miR-125 family (137). Reflecting changes in miR-125b expression in patients who experience biochemical failure, we separately revealed, in a cohort of 172 PCa patients, that Kaiso is overexpressed in a cohort of AA PCa patients in the...
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University of Alabama at Birmingham/TU cohort (138). As determined with another tissue microarray of 720 PCa patients from RPCI, NCOR2/SMRT expression also predicts progression risk. Similarly, miR-152 appears to regulate proteins involved in control of the epigenome. Ectopic expression of miR-152 results in decreased cellular proliferation, migration, and invasion, and decreased expression of DNMT1 through binding in the DNMT1 3’UTR (87) and thereby contributes to aberration of hypermethylation in AA tumors (87). Thus, our approaches support the concept that disease progression is influenced by miRNA in both EA and AA tumors and that increased aggressiveness of AA tumors may reflect both common and unique targetomes of mRNA networks. In particular, our studies have suggested that, within these targetomes, are mRNAs that encode for epigenetic regulators of DNA methylation and histone modifications. This suggests a complex interplay between upstream epigenetic regulation and downstream regulation of epigenetic regulators, which together determines disease risk.

In the AA PCa cohort of miRNAs, we have examined the impact of DNA methylation on some of the miRNAs. Validation of specific miRNAs by q-PCR across a panel of 11 cell lines demonstrated that miR-132, miR-367b, miR-410, and miR-152 were decreased in the more aggressive PCa cells, and expression of each miRNA was reversed after treatment of the cells with 5-aza-2’-deoxycytidine, suggesting a role for CpG methylation. Others have suggested that, in PCas, miR-132 is silenced by methylation (139). Our data confirm that miR-152 is silenced by methylation in PCas (87). In a comparison of normal/tumor ratios of miR-152 expression in 20 EA and 20 AA PCa patients, miR-152 expression was decreased in tumors of 67% of all patients, with 50% of the AA patients showing a difference, compared to only 35% of EA patients. We also found that miR-152 expression was lower in non-malignant tissues from AA patients compared to those of EAs, suggesting the presence of heritable differences in the control of miR-152 expression.

The impact of genetic variation on miRNA expression. In support of these heritable differences, three single nucleotide polymorphisms (SNPs) on chromosome 17 (rs1553754, rs11079828, and rs6504340) are associated with miR-152 expression at the genome-wide level, and differ in minor allele frequency by 28% on average in comparing the YRI and CEU populations (140, 141). In fact, the minor alleles at two of these SNPs for miRNA expression quantitative trait loci (miR-eQTL), rs1553754 and rs6504340, are different in the YRI and CEU populations. These differences in the frequency of alleles associated with miRNA expression are evidence that the difference in methylation rates in miR-152 could be driven by differences in genetic variation seen between African and European populations. In addition to this population-level evidence, through our work, we have identified rs12940701 (C/T) in miR152; the minor allele (T) has a relatively high frequency (26%) in the CEU population versus the YRI population (11%), suggesting that EAs have lower methylation rates due to the presence of a T nucleotide instead of a C nucleotide,

Figure 2. Inverse relationships between CpG methylation and expression of 18 miRNAs associated with TMPRSS2 fusion-negative disease across 333 localized tumors in the TCGA cohort (15) (p = -0.5-6).
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which is less frequent in the Yoruba population. Indeed, the number of publications that demonstrate an increased rate of methylation in AAs compared to EAs is growing, supporting the value of these miRNAs as diagnostic for AA PCa.

9. PERSPECTIVES

There is an urgent need to identify and characterize minimally-invasive diagnostic markers of PCa progression in TMPRSS2:ERG fusion-negative AA patients, as these patients are generally underserved. By use of AA cell cultures and publicly available datasets, we have undertaken a discovery phase of interrogating miRNAs that associate with aggressive PCa. Several fundamental questions remain as to the impact of methylation on silencing of miRNA expression in PCas, particularly in AA patients. Thus, validation of the capability of these miRNA serum biomarkers to predict aggressive PCa in AAs is required before these miRNAs can be considered for clinical application.

In preliminary studies, we have examined expression of these 18 miRNAs in the sera of EA and AA PCa patients with matched stage and grade of disease. In this pilot study, only one miRNA (miR-30c-5p) was undetected in PCa patient serum. Even within this small set of patients, however, several miRNAs were expressed at different levels in AA vs EA patients.

These findings suggest that epigenetic events affected by genetic variation differentially regulate miRNAs in AA PCa patients and are drivers of TMPRSS2:ERG-negative tumors. Identification of differentially methylated regions in AA and EA PCas will aid in defining a more personalized risk assessment of developing aggressive PCa, for not only AA men, but all men with TMPRSS2:ERG-negative tumors.

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