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REVIEW

Prostate Cancer in African American Men: The Effect of Androgens and microRNAs on Epidermal Growth Factor Signaling

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Abstract Prostate cancer (PC) is one of the leading causes of mortality amongst elderly men in the USA and is second only to lung cancer. African Americans (AA) are at an increased risk of developing PC and are more likely to die from the disease in comparison to Caucasian Americans (CA). Chromosomal alterations or genetic differences between AA and CA may account for the variances observed in PC progression. Importantly, mutations in the androgen receptor (AR) or the epidermal growth factor receptor (EGFR) may contribute to the disparity. Current studies are investigating the role of small nucleotide polymorphisms (SNPs) and microRNAs (miRNAs), which affect protein translation of the receptors by regulation of the 3′ untranslated region (UTR), which may enhance the progression of PC. However, these genetic differences have not been fully explored in prostates between the two ethnic groups. This review will highlight the current studies on the EGFR signaling pathway as well as the involvement of SNPs and miRNAs and relate them to variances observed in PC of AA and CA men. With an understanding of these differences, specific preventive and therapeutic strategies may be developed to target personalized medicine for prostate carcinogenesis.

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Introduction

Prostate cancer (PC) is currently the most prevalent and is the second most deadly form of cancer affecting males in the USA [1]. In a man's life, he has a 1 in 7 chance of developing PC, and about 1 in 36 men will die from the disease. If the prognosis of PC is confined to the prostate, 94 % of these patients are expected to live for at least 15 years after diagnosis. The prostate has distinct regions: the peripheral zone, transition zone (central zone), and the fibromuscular zone [2, 3] (Fig. 1), and adenocarcinomas primarily arise in the peripheral zone. Nine out of ten patients that are diagnosed with PC have acinar adenocarcinoma [4], which are glands in the prostate that develop cuboidal or columnar-shaped malignant cells in the form of acini and tubules. The remaining 10 % of PCs includes ductal adenocarcinoma, transitional cell (or urothelial), squamous cell, carcinoid, small cell, sarcomas and sarcomatoid cancers. Risk factors such as age and family history (genetics) play a significant part in increasing the probability of developing PC. African American (AA) men are nearly 1.6 times more likely to be diagnosed with PC than Caucasian American (CA) men and 2.4 times more likely to die from the disease [5]. These risk factors, especially genetic differences, aim at the need for the development of personalized medicine in the therapy of PC.

In 2015, the State of the Union address by U.S. President Barack Obama called for a national $215 million investment in precision medicine (Precision Medicine Initiative), which aimed to develop preventive and therapeutic strategies tailoring individual patient's needs. The development of cancer is a combinatory effect of environmental exposure and genetics, with the majority being linked to mutations to key essential

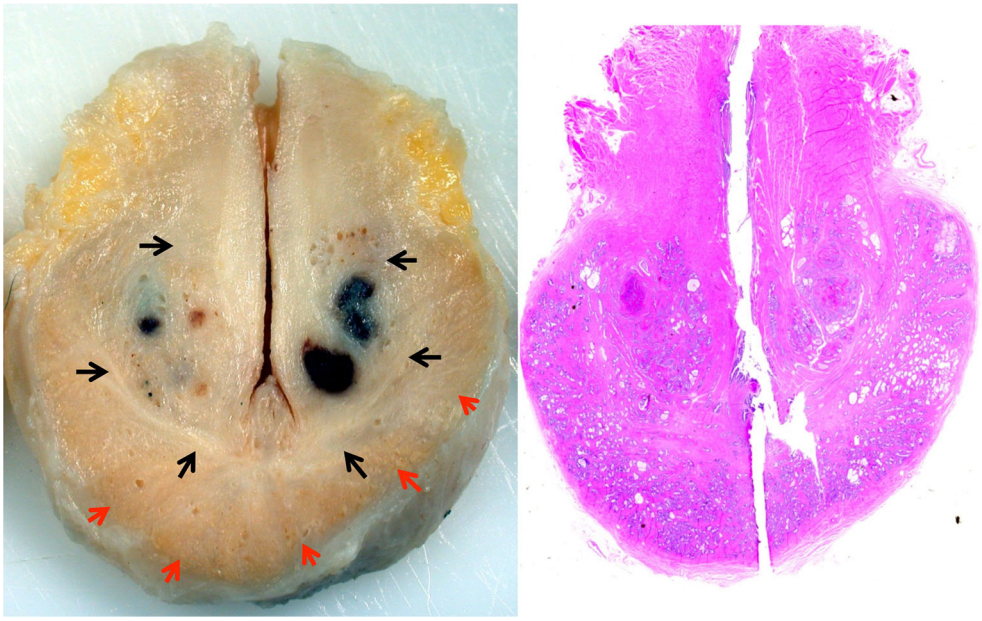

Fig. 1 Zonal locations of the human prostate. Gross photo and corresponding H&E of sagittal section of cadaver prostate illustrating visualization of the transition zone (*black arrows*) and the peripheral zone (*red arrows*). Whole prostate were surgically removed from organ donors, procured locally as part of the University of Toledo, Department of Urology's renal transplantation program

genes. In precision medicine, based on genome analysis, specific targeting of mutations to an individual may be used to tailor preventive and therapeutic strategies for the patient. Ultimately, reducing the notion that treatment for a particular disease is "one-size-fits-all." In prostate carcinogenesis, particularly, mutations in essential hallmark genes, such as the androgen receptor (AR), phosphatase and tensin homolog (PTEN), and the epidermal growth factor receptor (EGFR), are known to play an important role in the development of PC and may be differentially expressed in AA relative to CA men. For instance, EGFR is an oncogene that has been shown to be abnormally high in AA patients [6], which functions to enhance proliferation, migration, and cellular survival. Some studies have shown that microRNAs (miRNAs) might play a role in the mediation of cancer progression. However, the heterogeneity of miRNA regulation of EGFR in AA or CA men is unknown. In this review, we discuss differences in AA and CA prostate cancer cells and evaluate the regulatory mechanisms that EGFR, combined with targeting miRNAs, signals in PC between the two populations.

EGFR Signaling Cascade

EGFR may contribute to the genetic disparity seen between the two populations during prostate carcinogenesis. In 2004, Shuch et al. demonstrated that the expression of EGFR in prostate cancer is significantly increased in AA patients compared to CA patients [6] (Fig. 2). More recently, research has shown that the androgen-dependent MDA PCa 2b cells, which were derived from an AA patient, express more EGFR than the CA androgen sensitive LNCaP cells [7]. Treatment with EGF in AA-derived cell lines (MDA PCa 2a and MDA PCa 2b) stimulated cellular proliferation, and even greater growth was seen with combined treatment of dihydrotestosterone (DHT) and EGF; thus, demonstrating an interplay between AR and EGFR [8].

EGFR (also known as Her1 or ErbB1) belongs to the ErbB family of receptor tyrosine kinases (RTKs) and is typically activated by ligand binding such as EGF, transforming growth factor-α (TGF-α), amphiregulin, betacellulin, epigen, epiregulin, and heparin-binding EGF-like growth factor (HB-EGF) [9, 10]. Binding of ligand to EGFR on the extracellular domain causes a conformational change that exposes a receptor–receptor interaction site resulting in dimerization of two EGFR monomers (Fig. 3) [11]. EGFR can also

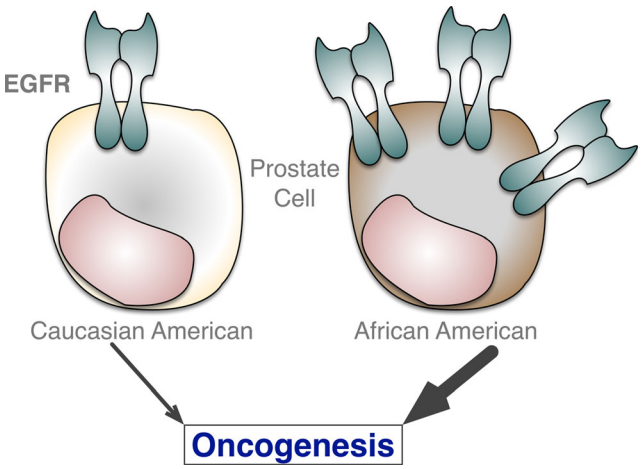

Fig. 2 EGFR expression in African American (AA) men compared to Caucasian American (CA) men. EGFR has been demonstrated to play a major role in prostate carcinogenesis, with increased expression in prostatic tissue. In AA, men, particularly, the expression of EGFR is higher than that of CA patients with PC, which increases oncogenesis [6]

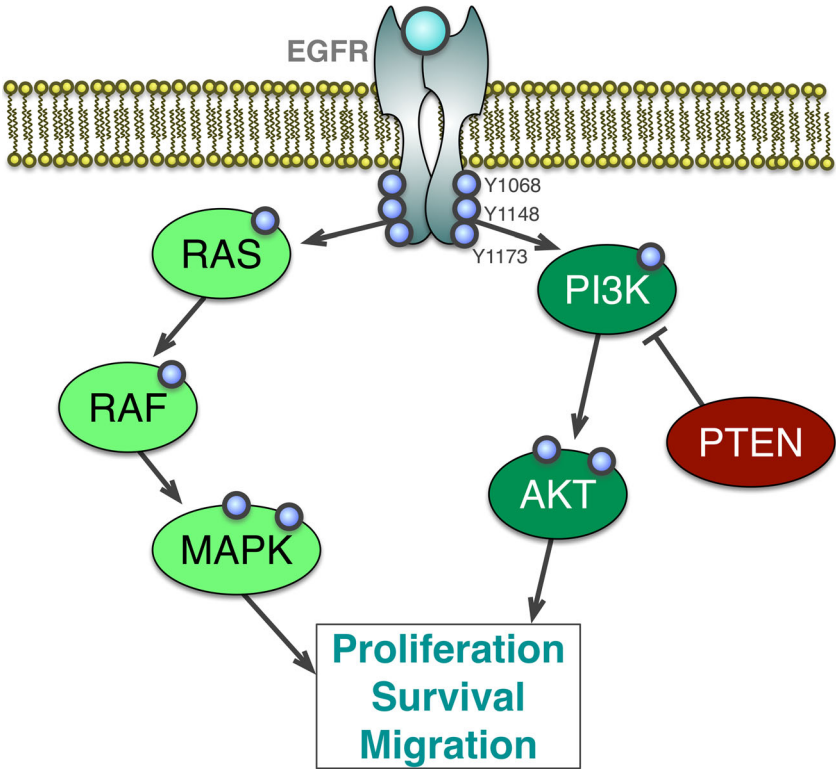

Fig. 3 Major epidermal growth factor receptor signaling pathway. Binding of EGF ligand causes dimerization of EGFR receptor, which causes autophosphorylaton of tyrosine residues at position Y1068, Y1148, and Y1173 on the C-terminal domain. This autophosphorylaton leads to activation of major downstream cellular pathway such as the Ras/Raf/mitogen-activated protein kinase (MAPK) pathway involved in cellular proliferation and phosphatidylinositol 3-kinase (PI3K)/AKT pathway that plays a role in cell growth, invasion and migration, and apoptotic resistance. In addition, phosphatase and tensin homolog (PTEN) inhibits the PI3K/AKT pathway via its dephosphorylation of phosphatidylinositol (3,4,5)-triphosphate (PIP3) to PIP2 (not shown)

heterodimerize with other RTK family members including ErbB2/Her2, ErbB3/Her3, or ErbB4. Overexpression of EGFR levels may also enhance signaling and dimerization, which may explain the reduced response to cellular proliferation with the EGFR inhibitor AG1478 in the AA MDA PCa 2b cells [7], which are known to have higher levels of the receptor [6]. The dimerization, whether homo- or hetero-dimerization, results in autophosphorylation of intracellular tyrosine residues at position 1068, 1148, and 1173 in the C-terminal domain leading to the initiation of multiple downstream signaling pathways. There are two major signaling arms for EGFR (similar to the insulin receptor [12]): (1) the Ras/Raf/mitogen-activated protein kinase (MAPK) cascade that leads to cellular proliferation [13–16] and (2) the phosphatidylinositol 3-kinase (PI3K)/AKT pathway that is involved in cell growth, invasion, migration, and resistance to apoptosis [17, 18].

Inhibitory to the PI3K pathway, PTEN mutations have been implicated in various tumors such as breast, colon, and prostate. PTEN dephosphorylates phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2, leading to the inhibition of the PI3K/AKT pathway (Fig. 3) [19]. The loss of PTEN due to mutation has been associated with cellular proliferation in PC [20]. Thus, this leads to the elevation of downstream activity of the PI3K/AKT pathway. Interestingly, the deletion of PTEN in AA men with PC was less frequent compared to that of CA men. In 2015, Petrovics et al. reported that PTEN deletions to be significantly less frequent in AA tumor samples (15 %) compared to CA samples (63 %) [21], which was also shown in a study by Khani et al. in 2014 [22]. Overall, these data suggest that the aggressiveness of PC in AA patients may not be contributed to PTEN. It is important to note that AA women with breast cancer have an increased risk of developing invasive cancer over CA patients [23]. A database of 2,567 breast cancer tumor samples revealed that more AA women were EGFR-positive [24]. However, there was no difference observed in PTEN expression when compared to non-African American women [23]. Therefore, it is likely that the increased EGFR expression in AA men enhances the disparity and not PTEN expression. Studies depicting the expression of both EGFR and PTEN in the same samples of prostate adenocarcinoma are lacking, but Muga et al. revealed in 2010 an 8.2 % prevalence of EGFR mutations and 3.3 % of PTEN mutations in a cohort of 98 prostate adenocarcinomas [25]. Though the occurrence is minor, it was the first study to show that both genes may play a major role in PC progression. Unfortunately, ethnicity was not taken into account in this study.

Crosstalk of Androgens and EGFR in PC of African Americans

AR is a member of the nuclear receptor family and consists of three functional domains: an amino-terminal activation factor-1 (AF-1) domain, a central DNA-binding domain (DBD), and

a carboxy-terminal ligand-binding domain (LBD; Fig. 4a). AR signaling is necessary for the development and maintenance of the male reproductive organs including the normal growth of the prostate gland. Almost 30 years ago, mean serum testosterone levels were reported to be higher in AA men in comparison to CA [26, 27]. In 2003, Gaston et al. showed that the expression of the AR protein in AA vs. CA patients undergoing radical prostatectomy was 22 % higher in benign prostate tissue and 81 % higher in malignant tissue [28]. Two polymorphic trinucleotide repeats (CAG and GGC) have been found in exon 1 of the AR gene [29]. The CAG repeats encode for a polyglutamine chain located upstream of the AF-1 domain, and as a result causes an adverse effect on AR function [30]. In particular, an inverse relationship exists between the number of CAG repeats and AR transcriptional activity. A shorter CAG repeat has been shown to have higher AR activity [30] and was shown to be associated with an elevated risk of developing PC [31–33]. Interestingly, studies have shown that AA men have significantly shorter CAG repeats in comparison to CA men [29, 34–36] (Fig. 4b), which may, in part, explain the AR variation between the two ethnic groups that potentially contribute to the disparity.

Early PC is androgen dependent, and as such, the first course of PC treatment is often through chemical castration by androgen ablation therapy to reduce testicular production of androgens [37, 38]. The androgen hormone ablation through the use of estrogen therapy (diethylstilbestrol), luteinizing hormone-releasing hormone receptor agonists (leuprolide, goserelin, histrelin, and triptorelin) and AR antagonists (degarelix), or bilateral orchiectomy is initially effective in controlling PC and its symptoms. Unfortunately, recurrence may occur, leading to castration-resistant prostate cancer (CRPC) [39]. There is currently no effective therapy to slow the progression of CRPC. PC cells in CRPC can continue to metabolize adrenal androgens (androstenedione and dehydroepiandrosterone) into testosterone and DHT. However, a nonconical signaling mechanism may activate AR-independent of androgens, which suggest that there are other partners involved in the AR pathway.

Studies have reported that EGFR can activate AR indirectly through an androgen-independent manner [40, 41]. The effect of EGFR signaling on AR with shorter CAG repeats in AA patients has not been investigated. However, AR has been shown to increase EGFR expression, which may be linked to the higher incidence of PC in AA patients. Pignon et al. showed that DHT treatment did not increase EGFR in androgen-insensitive cells, whereas it did in androgen-sensitive cells [42]. It is important to note that the expression of EGFR is higher in androgen-independent PC cells, compared to hormone sensitive cells [43–46]. When used in

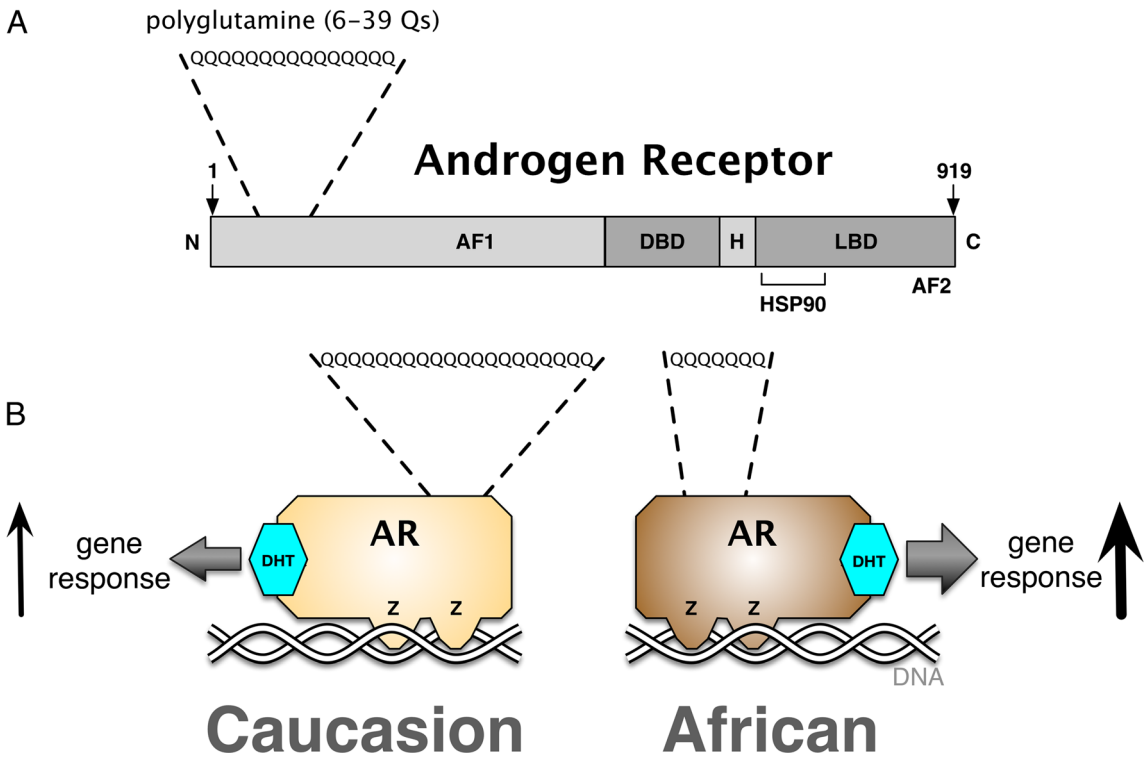

Fig. 4 AR gene structure and comparison of Caucasian and African American AR signaling. **a** Structural domains of the human androgen receptor (*AR*) and the polymorphic trinucleotide CAG repeats in exon 1 that encode for a polyglutamine chain located upstream of the activation factor-1 (AF-1) domain. *AF* activation factor, *DBD* DNA-binding domain, *H* hinge region, *LBD* ligand-binding domain, *HSP90* HSP90-binding region. **b** The polyglutamine (*QQQQ*) chain in the AR gene of Caucasian men is longer than African American and causes a reduced AR gene response. *Z* zinc finger, *DHT* dihydrotestosterone

combination therapies, androgen insensitive cells are more sensitive to EGFR inhibitors, PD168393 and ZD1839 [45]. However, the EGFR inhibitors erlotinib or AG1478 alone are not as active in androgen insensitive cells [7, 47]. Possibly due to the cell being less reliant upon the EGFR signaling cascade, as AR expression has been shown to lower the internalization of EGFR signaling [48]. In consideration of the studies as mentioned above, there is a relatively small proportion of the literature on EGFR and AR from recent years, which demonstrates the need for more current investigations addressing ethnic differences in PC.

Single Nucleotide Polymorphisms in the EGFR Gene

Differences in single nucleotide polymorphism (SNPs) can contribute to an individual's susceptibility to cancer and the aggressiveness of the disease. For example, genotyping of nine SNPs within the EGFR 3′-untranslated region (3′ UTR) found that one particular SNP to be associated with increased PC recurrence (SNP Ref: rs884419) [49]. Patients that have the A/A SNP in the 3′ UTR of EGFR were at increased risk of developing PC recurrence within 3 years after radical prostatectomy, in comparison to patients carrying the G/G or A/G genotypes (SNP Ref: rs884419) [49]. However, the functional role of this SNP is currently unknown. Also, investigating if this SNP is higher in the AA population is of value. Other SNP interactions with EGFR were found in three genes and shown to be associated with PC aggressiveness, which included matrix metallopeptidase (MMP16), roundabout homolog 1, and colony stimulating factor-1 (CSF-1) [50]. However, despite the investment made, the ethnicity of these SNP interactions with EGFR is unknown, and future research is needed.

Studies identifying SNPs in PC-related genes in various ethnic groups have not been adequately explored, especially SNPs in AA vs. CA patients. However, a study by Amundadottir et al. did find that the SNP on chromosome 8q24 (SNP Ref: rs1447295), with mutant allele A and ancestral allele C, to be correlated with increased PC risk [51], and Freedman et al. observed a stronger association in the AA population with PC [52]. Furthermore, Amundadottir et al. showed that in three groups of case–control men with a microsatellite marker on chromosome 8q24 (DG8S737) had a higher frequency in PC (13.1 %) compared to control (7.8 %) [51], which suggest that this location on the chromosome may have ethnic differences. Other studies have shown a sequence variant (11381 G/C) on the 3′ UTR of the toll-like receptor 4 (TLR4) gene to be a risk factor for PC in Sweden men (predominately white men) [53], thus, implicating a variation in PC aggressiveness in this population. One particular SNP (C/T mutation in the ancestral allele: C; SNP Ref: rs4054823), which does not contain any known gene, but has proximity to *HS3ST3A1*, a heparin sulfate biosynthetic enzyme, has been shown to have a frequency in different ethnic origins [C (0.30560002) and T (0.69440001) in Africans, C (0.44630000) to T (0.55370003) in Europeans, (1,000 genomes)]. It is important to consider that the TT SNP genotype (SNP Ref: rs4054823) has a higher frequency in aggressive PC patients when compared to a lower grade, suggesting that there is an inherited variant that potentially predisposes some men to higher disease states [54].

Despite the limited studies on SNP variants and PC of AA vs. CA men, the evidence presented show that there might be differences in genetic alteration between the populations. Moreover, SNPs in the 3′ UTR of microRNA (miRNA)-binding sites may potentially alter the regulation of specific genes. The 3′ UTR miRNA-binding sites may have SNPs that can lead to the PC disparity seen in AA men.

MicroRNAs and EGFR in PC

The past decade of investigations has revealed the importance of miRNAs in the regulation of gene expression during cancer development, progression, and metastasis. The miRNAs are small non-coding RNA sequences between 19 and 25 nucleotides that bind directly to the 3′ UTR of mRNA of the transcribed gene, which can cause early degradation of mRNA transcripts or impair translation [55], and recently, a few have been shown to positively affect gene expression [56]. Fortunately, there are several online programs that can predict miRNA-binding sites in the 3′ UTR of several genes. An in silico analysis of the human EGFR 3′ UTR using TargetScan (Human version 7.0) revealed several miRNAs that may potentially regulate expression (shown in Fig. 5). Confirming our analysis, Tao et al. showed that miR-133a/b inhibited the expression of EGFR by binding to its 3′ UTR in human PC, and caused a subsequent decrease in downstream effectors MAPK and AKT [57]. Similarly, in bladder cancer, miR-133a/b directly targets EGFR, causing inhibition of cell proliferation, migration, and invasion [58]. However, the expression of miR-133a/b in AA compared to CA patients is unknown. Also an inhibitor of proliferation and EGFR expression, miRNA-137 was shown to be downregulated in thyroid cancer, which increased invasion [59]. Interestingly, miR-148 has been demonstrated to increase the expression of EGFR [60], which may cause enhancement of EGFR expression in AA patients. However, the differential role of miR-148 in AA or CA patients has not been investigated in PC. Investigations of the PC samples or cells and the measurement of miR-133a/b, miRNA-137, and miR-148 would reveal if they are possibly involved in the predilection of AA patients in PC.

The expression of miR-144, also a predicted target of EGFR, was upregulated in high-grade tumors of PC [61]. Also, in nasopharyngeal carcinoma, the increased expression of miR-144 promoted growth by the repression of PTEN

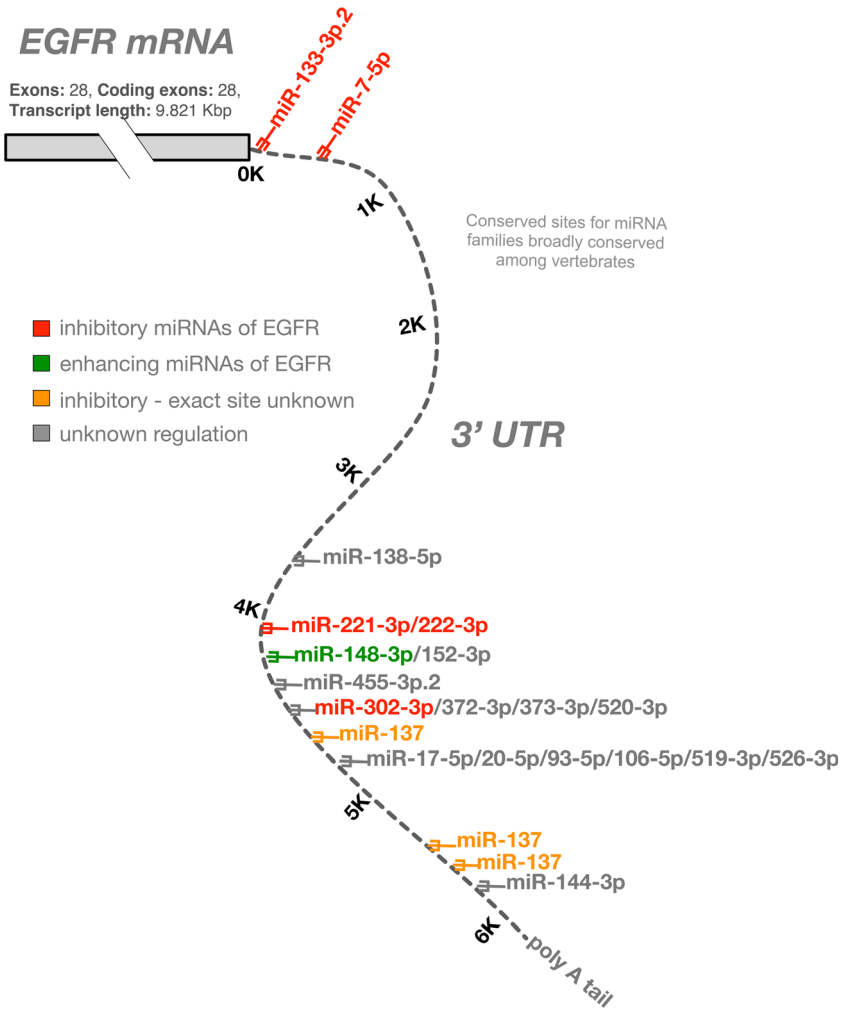

Fig. 5 miRNA-binding sites in the 3' UTR of human EGFR. In silico analysis of the hEGFR 3' UTR using TargetScan (Human version 7.0) predicted several miRNAs putative targets that may regulate EGFR expression. *Red* miRNA that inhibits EGFR, *green* miRNA that increase EGFR, *gray* miRNA that has unknown function on EGFR expression

leading to the activation of the PI3/AKT pathway although this inhibitory mechanism was independent of EGFR [62]. We have recently shown that miR-144 increases the expression of the glucocorticoid receptor β (GRβ) during migration of bladder cancer cells [63]. We have also shown that GRβ binds directly to the PTEN promoter to inhibit expression [64], which may be the role that is mediated by miR-144 in carcinomas. However, miR-144 regulation of EGFR or GRβ in AA and CA patients is unknown. Also a direct target of the 3′ UTR of EGFR, miR-7 directly inhibits EGFR in glioblastoma, breast cancer, and prostate cancer cells by decreasing mRNA and protein levels, which negatively regulates the downstream EGFR effectors AKT and ERK [65]. Additionally, Kefas et al. reported that miR-7 inhibits EGFR and AKT, thereby decreasing cell viability and invasiveness in glioma cells [66]. In opposition, EGFR signaling positively regulates miR-7 transcription in Drosophila during photoreceptor differentiation [67], which may function as a negative feedback loop for EGFR. Both miR-144 and miR-7 may be novel targets in PC, and investigations of their role in AA and CA patients are needed.

The prognostic biomarker of miRNA in PC has been demonstrated by a series of studies examining prostate specimens of patients that underwent radical prostatectomy. Tong et al. measured miRNA expression by qRT-PCR analysis from 40 patients and showed that 16 miRNAs were associated with biochemical recurrence within 2 years after surgery [68], which included upregulation of known targets of EGFR miR-20 and miR-302 as well as downregulation of miR-221 and miR-222. EGFR expression has been shown to be inhibited by miR-302 in human hepatocellular carcinoma cells [69], but differences in AA patients have not yet been analyzed. Additionally, the expression of miR-221 was downregulated in 92 patient samples, which correlated with tumor progression and clinical recurrence [70]. In particular, miR-221 inhibition of EGFR expression causes a downstream effect on the Ras-Raf-Mek pathway resulting in apoptosis [71]. As such, miR-221 could be a stronger predictor of clinical recurrence of PC [70]. However, Srivastava et al. examined the expression levels of miR-221 between AA and CA populations and found no difference [72], but the study did find that miR-99b was significantly lower in AA patients compared to

CA. This could potentially contribute to the aggressiveness of PC seen in the AA population, but the role of miR-99b is unknown.

Although not targets of EGFR, other studies have found that there may be potential differences in miRNA expression between AA vs. CA patients. Theodore et al. found that miR-26a to be differentially expressed in AA PC cells with a 13.13-fold increase in malignant cancer [73]. Another study by Calin and Croce revealed that miR-301, miR-219, miR-26a, miR-1b-1, and miR-30c-1 are differentially expressed in PC from AA in comparison to CA patients [74]. Furthermore, Theodore et al. evaluated the expression of miR-152 in PC tissues with matched controls and observed that 50 % of AA patients had a significantly lower miR-152 expression in comparison to 35 % of CA patients [75]. Of importance, decreased miR-152 expression is correlated with increased metastasis and decreased disease or recurrence-free survival [75]. The differential regulation of miRNAs that exists in AA and CA men with PC may explain the disparity and could potentially serve as diagnostic or prognostic tool to tailor specific preventive therapies.

Conclusion

There is an ethnic divergence between African and Caucasian American populations in regards to prostate cancer acquisition and progression. The specific genetic mechanisms governing this discrepancy have not been fully explored. EGFR may play a significant role in PC progression in both populations, especially in AA men, as EGFR is increased in these patients. Furthermore, investigating the miRNAs and SNPs that regulate EGFR may strengthen our knowledge between the PC disparities between the populations. An understanding of the specific EGFR regulatory mechanisms between the two populations may lead to novel drug therapy that can be employed to aid prostate cancer treatment in AA men, thus implementing precision medicine at its core.

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Compliance with Ethical Standards

Conflict of Interests The authors declare that there is no conflict of interests regarding the publication of this paper.

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