Racial disparities in prostate cancer: a molecular perspective

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1. ABSTRACT

Prostate cancer incidence and mortality rates are remarkably higher in African-American men as compared to their European-Americans counterparts. Despite these recognitions, precise causes underlying such prevalent racial disparities remain poorly understood. Although socioeconomic factors could account for such differences up to a certain extent, it is now being increasingly realized that such disparity has a molecular basis. Indeed, several differences, including genetic polymorphism, gene mutations, epigenetic modifications, miRNAs alterations, etc., have been reported in malignant prostate tissues from patients of diverse racial backgrounds. Here, we attempt to provide a molecular perspective on prostate cancer racial disparities by gathering available information on these associated factors and discussing their potential significance in disproportionate incidence and clinical outcomes.

2. INTRODUCTION

Prostate cancer is one of the most commonly diagnosed malignancies among men worldwide and remains the second leading cause of cancer-related death in the United States. According to an estimate by the American Cancer Society, 180,890 new diagnoses of prostate cancer will be made in 2016, and nearly 26,120 patients will die due to this malignancy (1). Recent data suggest that the prostate cancer incidence is declining, but the overall prostate cancer-related mortality continues to rise among African-American (AA) men (2).

Epidemiological data suggest that the AA men are disproportionately affected with prostate cancer compared to European-Americans (EA). The overall prostate cancer incidence and mortality are remarkably higher in AA compared to EA men (3). According to publish data, AA men are 1.6 times more susceptible to develop prostate cancer, and about 2 times more likely to die from this disease than EA men. In fact, the disparity in mortality rate between AA and EA men is higher for prostate cancer than that for any other malignancy (2). In general, AA men are often diagnosed with more advanced and aggressive prostate cancer compared to any other racial/ethnic groups. However, the observed greater mortality rates in these men can only partially be explained by the characteristics of tumors at the time of diagnosis (4).

So far, several studies have been conducted to investigate the molecular and biological bases of prostate cancer racial disparities, yet precise underlying causes
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remain largely unclear. It is commonly believed that access to health care, cultural and socioeconomic factors, diet and preventive health factors, such as awareness and motivation for prostate cancer screening, contribute significantly to prostate cancer racial disparities (5, 6). However, a growing body of evidence now suggests that biological factors, such as differences at the genetic and molecular level could be more crucial than thought for racial disparities in prostate cancer incidence and outcome (7). In this review article, we have discussed molecular differences in prostate cancers of AA and EA men, and highlight potential roles for such variations in racially disparate clinical outcomes.

3. SOCIOECONOMIC AND BEHAVIORAL FACTORS CONTRIBUTING TO RACIAL DISPARITIES IN PROSTATE CANCER

The clear-cut underlying causes for racial disparities associated with prostate cancer are not fully understood. However, several non-biological and/or biological risk factors such as socioeconomic status, lack of access to care, diet, age, lifestyle, family history and hormones, molecular alterations have been implicated as contributing factors to the race-specific prostate cancer incidence and clinical outcome. Epidemiological studies indicate that socioeconomic status (SES) of AA men is an important factor for higher mortality and morbidity associated with prostate cancer (5, 6). However, significance of SES in prostate cancer racial disparity is debatable as no difference in prostate cancer recurrence after radical prostatectomy was observed among lower income AA patients as compared to AA patients of middle income group (8). Although lack of access to health care due to low health insurance rates or financial condition in AA men relative to EA men could very well be responsible for their enhanced prostate cancer burden and poor outcome, non-financial barriers including poor health consciousness, not believing in the health care system, fear of the diagnostic and/or treatment strategies etc., have also been suggested as major factors for late diagnosis. Significant evidence suggests that dietary habits such as consumption of alcohol, animal origin saturated fats, selenium, vitamin D, vitamin E, lycopene and isoflavones are also associated with prostate cancer racial disparities (9). Vitamin D insufficiency is a common public health problem in the United States and has been associated with prostate cancer mortality (10). AA men have low serum level of vitamin D than EA that might make them more susceptible to prostate cancer (11). In addition, family history and quality of life are other factors responsible not only for prostate cancer risk in specific race, but also for overall clinical outcomes (12).

4. MOLECULAR BASES OF PROSTATE CANCER RACIAL DISPARITIES

Although the difference in socioeconomic factors may be responsible for racial disparities associated with prostate cancer, it is being increasingly recognized that these disparities have a molecular basis as well. In fact, enhanced incidence and mortality in AA men with prostate cancer have been observed as compared to EA counterparts even when socioeconomic factors have been accounted for (3, 5). A number of molecular factors specific to tumor cells, including gene-polymorphism, -mutations, epigenetic alterations, overexpression and/or suppression of miRNAs and growth promoting-suppressing proteins, have been associated with racial disparities (Figure 1). Moreover, emerging evidence also suggests the participation of tumor-microenvironment-associated inflammatory signaling molecules in racially disparate clinical outcomes in prostate cancer.

4.1. Genetic factors associated with prostate cancer racial disparities

With the help of advanced molecular biology techniques, the insight into the genomics of prostate cancer has grown immensely. Several race/ethnic-specific genetic abnormalities have been identified in prostate cancer. In the subsections below, we discuss current knowledge about these genetic alterations and their possible association with observed prostate cancer racial disparities.

4.1.1. Genetic polymorphism

Genetic polymorphism is one of the critical determinants for the disease susceptibility and therapeutic outcome. Ledet et al. performed linkage analyses on 241 individuals from 20 large AA families and identified 12q24 and 2p16 loci to be dominantly linked with prostate cancer susceptibility (13). In a genome-wide association study using a set of ancestry informative markers in 1,060 AA and 1,087 EA men with prostate cancer, it was identified that four SNPs (rs2660753, rs13254738, rs10090154, rs2735839) were associated with aggressiveness of prostate cancer in both AA and EA men (14). Data also suggested that in AA patients, three SNPs were associated with prostate specific antigen (PSA) levels, which was not the case in EA patients. Moreover, it was also reported that two other SNPs (rs266870 and rs2735839) were associated with stage and Gleason scores. In three case-controlled studies of European ancestry men from Iceland, Sweden and the USA, Amundadottir et al. identified allele 8 of microsatellite DG8S737 to be associated with prostate cancer. Moreover, their study revealed that about 13% of the healthy population and 19% of prostate cancer patients carried at least one copy, resulting in 8% increase in population-attributable risk (PAR). In addition to this, their study revealed that in AA men, about 30% healthy population and 41% of patients were carriers with about 16% estimated PAR, which could likely contribute to higher incidence of prostate cancer in this population relative to men of European ancestry (15).
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The enzyme products of CYP3A4 and CYP3A43 are well known to play a role in testosterone metabolism and have been associated with prostate cancer occurrence and aggressiveness (16). Johnson and coworkers observed significant CYP3A4 allele variations in different racial groups. AA men exhibited higher frequencies of the CYP3A4*1B allele as compared to EA men in both cases and controls. Interestingly, CYP3A4*1B allele polymorphism was inversely associated with the development of prostate cancer in EA men (16,17). Furthermore, significant differences in the CYP3A5 and CYP3A43 allele frequencies were also observed among both AA and EA men with significantly higher CYP3A5*1 and CYP3A43*3 allele frequencies reported in AA men. The presence of the CYP3A4*1B-CYP3A5*1 genotypes (i.e. both variants) was positively associated with prostate cancer in AA men (16). By performing the pairwise interactions study with CYP3A4*1B and CYP3A43*3 alleles, authors reported their significantly greater protective effects for early onset of prostate cancer. EA carried 4.0. % of this allelic combination, while higher frequency (35.0. %) of this haplotype was observed in AA samples. This clearly suggests that this haplotype may have its greatest impact in AA. It is likely that AA men carrying the CYP3A4*1B and CYP3A43*3 combination will have lesser early prostate cancer diagnoses (16).

Arg462Gln gene variation is very common among AA cases compared to the controls. In family-history positive EA, Arg462Gln was positively associated with low-grade and early-stage disease. While in family-history positive EA, Arg462Gln was positively associated with low-grade and early-stage disease. Further analysis on AA population group suggested that Arg462Gln was associated with positive family history and high-stage disease (18,19).

Critical role of androgen receptor (AR) signaling in prostate cancer pathobiology has been very well documented (20). Exon encoding aminoterminal transcriptional domain of AR consists of two polymorphic repeats of high frequency, CAG and GGN. It is reported that the length of CAG repeats is different in AA (average 19-20) and EA (average 21-22) races. Studies conducted over CAG repeats polymorphism have shown that shorter-length CAG repeats increases the prostate cancer disparity in AA men (21,22). Thomas et al. reported two SNPs (rs4242382 and rs983267) in 8q24 region and one SNP (rs4430796) in HNF1B region of chromosome. They also observed two SNPs (rs10896449 and rs10486567) over 11q13 and JAZF1 region of chromosome 11 and 7, respectively. These SNPs made them susceptible for the incidence and faster progression of prostate cancer (23). Chang et al. validated the genome-wide prostate cancer association in AA men and identified SNPs associated with aggressive form of disease. These SNPs were present on chromosome 8q24 (rs9811122, rs7000448 and rs16901896), chromosome 10 (rs7904463) and chromosome X (rs5945572) (24).

4.1.2. Gene mutations

In addition to gene polymorphism, mutations in several genes are also considered as important genetic factors contributing to racial disparities in prostate cancer. Kittles et al. studied the significance of mutation in the EPHB2 gene, which encodes the EphB2 receptor tyrosine kinase, for prostate cancer prevalence in AA men in a case-controlled study (25). They reported that the frequency of the K1019X (3055A→T) nonsense mutation in the EphB2 gene differed between AA and EA prostate cancer cases. Higher frequency of the K1019X (3055A→T) nonsense mutation and the higher prevalence of prostate cancer among AA men was reported as compared to EA. K1019X (3055A→T) nonsense mutation was present in AA prostate cancer at a higher rate (15.3%) as compared to EA cases (1.7%). In addition, higher frequency of the K1019X (3055A→T) nonsense mutation was associated with higher prevalence (> 2.0. fold) of prostate cancer among AA men relative to EApientes. These data confirm that K1019X mutation in EphB2 gene is an important genetic risk factor for the prostate cancer.
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4.2. Epigenetic changes in prostate cancer racial disparity

In addition to the genetic alterations, prostate cancer cells also carry epigenetic modifications, which affect a number of molecular and cellular events associated with development, progression and therapeutic outcome. Abundant evidence has accumulated to suggest that epigenetic alterations are significantly different in the prostate tumors of AA and EA men.

DNA methylation, the addition of a methyl group to the cytosine within cytosine guanine dinucleotides (CpGs), is considered the most frequent epigenetic modification. DNA methylation ultimately causes gene silencing by blocking the access of transcriptional factors and/or activators to the target sites (28). Several studies have demonstrated that the methylation rate of several genes in normal and malignant prostate tissue is race-specific, which may potentially contribute to the racial disparity associated with prostate cancer (29-31). Kwabi-Addo and co-workers examined the methylation pattern of six different genes (GSTP1, AR, RARB2, SPARC, TIMP3, and NKX2-5) in prostate tissue specimens from AA and EA males. They observed significantly higher methylation for all genes, except GSTP1, in the AA samples in comparison to that from EA prostate cancer patients. In addition, two genes (NKX2-5 and TIMP3) were hyper-methylated in normal prostate tissue samples of AA racial background as compared to those from EA (29).

Woodson et al. examined racial differences in the methylation status of the GSTP1, CDH1, ANXA2, CD44, RARB2, RASSF1, CAV1 and EDNRB genes in prostate tumors (30,31). Higher frequency of CD44 methylation among AA relative to EA was observed (30,31). Comparison of GSTP1 methylation in prostate cancer samples with their clinical and pathological outcomes showed that AAs with GSTP1 methylation were 13.3 times more likely to have prostate cancer, whereas in Europeans, this ratio was only 3.8 (32). These findings suggested that methylated GSTP1 could be a putative biomarker for prostate cancer diagnostics in AAs. By contrast, Das et al. observed that the CD44 and GSTP1 were not significantly different in terms of their methylation status between populations. However, significantly enhanced methylation of PYCARD (TMS1/ASC) in benign prostatic hyperplasia (BPH) was reported in AA cases (33). Despite these contradictory findings, the importance of epigenetic modifications cannot be undermined. Future studies in this area may be useful for understanding the molecular basis of race-associated disease, as well as in identifying biomarkers to better detect and assess prostate cancer in a particular ethnic group.

4.3. MicroRNAs

MicroRNAs (miRNAs or miRs) are small, endogenous, non-coding RNAs of 18-25 nucleotides that act as important regulators of gene expression. miRNAs either degrade the target mRNAs or inhibit translation upon binding to the complementary regions in the 3' untranslated region (UTR) of the target mRNAs (34). Emerging data suggest that miRNAs play critical roles in tumor development, progression and therapy-resistance (34-36). An aberrant expression of several miRNAs has been observed in different tumors types including prostate cancer. miRNAs either promote tumor progression (oncomirs) or suppress their growth (anti-oncomirs or tumor suppressor miRs) (35,36). Recently, role of miRNAs in racial disparities associated with prostate cancer has also been observed. Five miRNAs viz. miR-1b-1, miR-26a, miR-30c-1, miR-219 and miR-301 were shown to be differentially-expressed in prostate tumors of AA and EA racial backgrounds (37). Later, Theodore et al. examined the expression of miR-26a in prostate cancer cell lines of AA (RC77N/E, RC77T/E and MDA-2PCa-2b) and EA (PrEC, RC-92a and PC-3) origin, representing non-malignant, malignant, and metastatic prostate cancer tumors, respectively (38,39). They observed increased (2.2. to 13.3. folds) expression of miR-26a in AA prostate cancer cells of all three stages and grades, when compared with EA cell lines of similar clinical stage and pathological-grade. Interestingly, there was an increasing trend in miR-26a expression toward the more aggressive prostate cancer cell lines in bases of both AA and EA origin. Differential-expression of let7c and miR-30c in prostate tumor tissues from AA and EA patients has also been reported (40). In a recent study, Wang et al. identified 22 miRNA signatures in AA and 18 miRNAs in EA prostate cancer. In addition, they also identified novel AA-specific enriched miRNA–mRNA pairs, including miR-133a/MCL1, miR-513c/STAT1, miR-96/FOXO3A, miR-145/ITPR2, and miR-34a/PPP2R2A. Computational pathway analysis suggested that miRNA–mRNA pairs predict the enhanced activation of EGFR–PI3K–AKT signaling in AA compared with EA cancers. Loss of function of these miRNA–mRNA pairs in AA prostate cancer cells reduced their proliferation, aggressiveness and increased docetaxel-induced cytotoxicity, while their converse manipulation in EA cell lines enhanced their aggressive potential (41).
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5. ROLE OF ABERRANTLY-ACTIVATED SIGNALING PATHWAYS IN PROSTATE CANCER RACIAL DISPARITIES

Several lines of evidence suggest that aberrant activation of various oncogenic pathways is associated with prostate cancer racial disparities. Below we have discussed in length about significance of these pathways.

5.1. Hormone-receptor signaling pathways

Androgens are hormones that are critical for normal male sexual development. Upon binding to androgen receptor (AR) within cells, androgens regulate the expression of several androgen-responsive genes. AR is an intracellular hormone receptor and a transcription factor, which is widely known to play critical roles in the development and progression of prostate cancer. Moreover, emerging data also suggest that AR signaling pathway is one of key biological mechanisms associated with prostate cancer racial disparities. It has been reported that AA men have higher serum testosterone levels than EA men, which may be related to the higher risk of prostate cancer in these men. In fact, high levels of androgens have long been considered as risk factors for prostate cancer development. Studies have suggested genetic mutations in an isozyme form of 5α-reductase (encoded by the SRD5A2 gene) to contribute to higher conversion rate of serum testosterone to dihydrotestosterone as another mechanism underlying prostate cancer racial disparities. Moreover, Gaston et al. have reported that expression of AR is 22% higher in benign prostate of AA men than those of EA (42). Interestingly, their study also revealed that its expression was 81% higher in malignant prostate tissue of AA patients as compared to that in EA counterparts. Using microarray and subsequent IPA analysis, 1,169 genes were identified to be differentially-expressed between AA prostate cancer and their matched normal prostate. Further, ARA55, GNAO1, GN3, POLR2L, PKCE, PRKD1, and TBP were among the highly upregulated genes, while the expression of CALR was down-regulated (43). Additionally, these data yielded a significant overrepresentation of the genes of AR signaling pathway. Gene fusions involving regulatory sequences of androgen-responsive gene promoter region of TMPRSS2, and coding sequences of ETS gene family resulted in androgen-dependent upregulated expression of ERG in prostate cancer (44). This prevalence of TMPRSS2-ERG gene fusion was significantly different in AA and EA prostate cancer cases being more common in AA prostate cancer cases. Growing body of evidence also suggests the role of estrogens in the development and progression of prostate cancer. Circulating levels of estradiol and precursor of estradiol "esterone" are elevated in AA relative to EA men. Considering that AA men have greater risk for prostate cancer development as compared to EA, increased circulating estrogens might suggest an association through the aberrant activation of ER pathway (45,46). This hypothesis is strongly supported by studies in which it was demonstrated that following chronic administration of testosterone to rats at low doses, prostate tumors developed at low incidence. However, when estradiol was given together with low-dose testosterone the incidence of prostate tumor development increased to nearly 100% (47).

5.2. Growth factor receptor signaling pathway

Several growth factor receptors, which are known to promote tumor growth, have also been identified as potential causes of racial disparities in prostate cancer. Enormous data is available to suggest a role of epidermal growth factor receptor (EGFR) signaling in prostate cancer carcinogenesis making it as a promising therapeutic target (9). In fact, studies also document the critical involvement of EGFR signaling pathway in androgen-independent progression of prostate cancer. Inhibitors of EGFR have been proven to impede the growth of both androgen-dependent and androgen-independent prostate cancer xenografts (48,49). Reports also indicate that EGFR is linked to prostate cancer racial disparity through intronic dinucleotide repeats (CA) and its overexpression (50,51). It was demonstrated that the longer allele of EA repeats is frequent in Asian individuals with 80% decrease in EGFR protein levels in comparison to shorter allele (51). In another study, Di Lorenzo reported that EGFR overexpression was more frequent in AA than EA patients (52). Later, it was demonstrated that in AA prostate cancer patients, EGFR is significantly overexpressed relative to EA patients suggesting that it might have an impact on the design of anti-EGFR therapeutic strategies in AA patients (9).

Insulin-like growth factors (IGFs) are growth-promoting hormones that play a crucial role in cell proliferation, differentiation, and apoptosis. IGFs exert their effects by binding to the IGF-1 receptor. Numerous studies have reported higher systemic concentrations of IGF-1 among AA compared with EA (53). The physiologic basis for higher IGF-1 among AA is not yet known. A simple explanation could be that AAs secrete more growth hormones in general for some undefined reasons. Nonetheless, higher IGF-1 expression has been associated with higher intake of total energy, carbohydrate, fat, and protein (53). Moreover, adiposity and physical activity may also influence IGF-1 levels, which is suggestive of influence of dietary habits on prostate cancer disparities (53).

5.3. Inflammatory signaling pathways

The tumor microenvironment (TME) typically consists of immune cells, adipocyte, blood vessels, and secreted soluble and insoluble factors such as cytokines, growth factors and an interconnected network of stromal fibroblasts. As a result, there is continuous bi-directional cross-talk between the tumor and stromal cells, which facilitates growth-promoting inflammatory signaling. Moreover, this signaling could also potentiate...
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Even though very few studies have been performed to investigate the significance of inflammatory TME in prostate cancer racial disparities, we have some strong evidence in the literature suggesting that there is disparate inflammatory TME in prostate cancer of AA and EA racial backgrounds (8,11). Histological analysis of prostate biopsy specimen from AA and EA patients revealed that significantly higher proportion of biopsy specimens of AA racial background (35.5% of 493) had infiltration of immune cells than that from EA men (28.0% of 736) (58). Levels of PSA were higher in both groups that had prostate inflammation as compared to those without inflammation (58). Wallace et al. performed the microarray analysis to study the gene expression profile of primary prostate tumors resected from patients of AA (n=33) and EA (n=36) racial background. They found several differentially-expressed genes in prostate tumor samples of AA and EA patients (59). Furthermore, bioinformatics analysis revealed that most of the differentially-expressed genes, including those encoding for autocrine mobility factor receptor (AMFR), chemokine receptor 4 (CXCR4), and matrix metalloproteinase 9 (MMP9), were associated with immune response, stress response, cytokine signaling, chemotaxis, and inflammation or tumor-immunobiology (59). In another microarray-based study, it was shown that genes associated with immune-related pathways, including IL1B, IL6, and IL8, were overexpressed in prostate cancer tissues from AA men compared to those from EA men (60). In addition, many stroma-associated genes were also found to be differentially-expressed in AA tumors relative to EA tumors. In stromal compartment, the altered genes were mainly linked with cytokine signaling molecules, including several interleukins, TGF-β, MIF and oncostatin M, thus implying that immune effectors released from stromal cells may also possibly define prostate cancer racial disparities (60). Enhanced mRNA expression of CXCR4, IL-6, IL8, IL1B, and TGFB1 was also reported in prostate tumor specimens of AA racial background as compared to EA cases. Differential levels of inflammatory cytokines have been detected in serum from prostate cancer patients of different racial groups. Serum IL-6 positively correlates with tumor-burden, disease aggressiveness, therapy-resistance, and poor progression of primary prostate tumors.
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clinical outcome of prostate cancer patients (61,62). In several studies, it has been reported that AA men have higher IL-6 levels than EA men, which suggests that IL-6 may be one of the key determinants of high prostate cancer morbidity and mortality in them (63-65). Together, these studies suggest that disparate inflammatory microenvironment may also underlie disproportionate incidence and unfavorable outcomes in AA men.

6. CONCLUSIONS AND FUTURE PERSPECTIVES

With increasing awareness and dedicated governmental support, research on understanding and eliminating the causes of racial disparities in cancer and other benign diseases is gaining momentum. Indeed, in many academic health centers, health disparity research has become one of the priorities. This increasing focus has resulted in an influx of data on various aspects of prevalent health disparities including that in prostate cancer. It is now well recognized that men of African descent experience greater incidence and mortality rates of prostate cancer as compared to men of other ethnicities and these disparity gaps continue to rise. At the same time, we have also developed a better understanding of the underlying causes associated with prostate cancer racial disparities. The data now strongly support that besides differences in socioeconomic status, genetic and non-genetic biological factors play an important role in racial disparities associated with prostate cancer. In fact, a number of genetic and epigenetic aberrations have been associated with racial disparities. However, exact link of these aberrations as causal factors remain yet to be established. Importantly, emerging evidence now also suggests differential tumor-microenvironment may also be one important cause for racially disparate clinical outcomes in prostate cancer patients, since the composition of tumor microenvironment can differ from patient to patient as a result of the genetic makeup of tumors, extent of genetic heterogeneity, host genetics as well as lifestyle, dietary and environmental factors. Therefore, it can be postulated that biological differences in tumors or more specifically, in tumor-microenvironment, are determined not only by host and tumor genetics, but also by socioeconomic, cultural, and behavioral aspects of the patients (Figure 2). This gives us a broader and more inclusive perspective of biological basis of prostate cancer racial disparities, and should direct our future endeavor in basic, clinical and translational research. As is always the case with any type of research, availability of relevant resources, funding support and appropriate research tools are vital to make progress in prostate cancer health disparity research. Thus concerted efforts at the research team level, community level, in clinics and by our policy makers are needed to make race-associated disparities as a thing of the past or at the least make them irrelevant in clinical practice.

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