Racial disparities: disruptive genes in prostate carcinogenesis

Savita Singh[1,2], Alexis Plaga[1,2], Girish C. Shukla[1,2]

[1]Department of Biological Sciences, Cleveland State University, Cleveland, Ohio, USA, [2]Center for Gene Regulation in Health and Disease, Cleveland State University, Cleveland, Ohio, USA

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1. ABSTRACT

Population specific studies in prostate cancer (PCa) reveal a unique heterogeneous etiology. Various factors, such as genetics, environment and dietary regimen seems to determine disease progression, therapeutic resistance and rate of mortality. Enormous disparity documented in disease incidences, aggressiveness and mortality in PCa among AAs (African Americans) and CAs (Caucasian Americans) is attributed to the variations in genetics, epigenetics and their association with metabolism. Scientific and clinical evidences have revealed the influence of variations in Androgen Receptor (AR), RNAse L, macrophage scavenger receptor 1 (*MRS1*), androgen metabolism by cytochrome P450 3A4, differential regulation of microRNAs, epigenetic alterations and diet in racial disparity in PCa incidences and mortality. Concerted efforts are needed to identify race specific prognostic markers and treatment regimen for a better management of the disease.

2. INTRODUCTION

Prostate cancer is the most frequently diagnosed malignancy affecting men in the United States and the second leading cause of cancer related deaths among men. According to the Surveillance, Epidemiology, and End Results (SEER) program the incidences of prostate cancer among different races vary greatly, with African Americans indicating the highest incidence rates of 31% (1). Furthermore, a large percentage of AAs develop more aggressive form of the disease in response to therapeutics and exhibit 28% higher mortality per 100,000 case, therefore signifying a distinct disparity issue. A number of interracial genetic differences predispose AAs to variation in cancer prognosis. Studies illustrating genome wide meta-analysis of different races has indicated variability in PCa susceptibly genes including but not limited to, Androgen Receptor (AR), macrophage scavenger receptor 1 (*MRS1*), RNAse L, cytochromes (CYP) and regulatory noncoding microRNAs. These genetic differences and variation in metabolism together with epigenetic variability also contributes to the divergence in the nurturing cellular niche, which determines the metastatic potential of PCa. This is evident from the association between disparity of tumor micro-environment and higher incidences of metastatic cancer in AAs. In addition to the genetic variation, disparity in treatment and socio-economic status also contributes to race specific

prognosis consequently, mortality. Therefore, it is of great importance to identify the potential cancer promoting genetic and epigenetic variations in races and to examine their exact contribution in observed disparity in PCa incidence. The leading focus of this report is to address race specific association between PCa progression, mortality and some genetic, epigenetic and lifestyle related differences between AAs and Caucasian Americans.

3. MAJOR GENETIC VARIATIONS IN PROSTATE CANCER LEADING TO DISPARITIES

3.1. Genetic heterogeneity in AR CAG repeat length and racial variation

Among many prostate cancer causative genes, Androgen Receptor (AR) contributes to enormous heterogeneity, and the length of the CAG repeats coded by exon 1 has inverse correlation with the transactivation function of AR (2). Majority of studies suggest a positive association between shorter CAG repeat lengths and progression of PCa (1) . A CAG repeat length of 22 or shorter has been implicated in a greater risk of developing PCa and AAs tend to have shorter CAG repeats. Mean AR gene CAG repeat length for CAs was found to be 21.9. versus 19.8. for AAs indicating that the shorter CAG repeats in AAs may contribute to the greater risk of PCa (3). Evidence show that CAG repeats are found in allelic association with other polymorphisms in the AR locus. One of these allelic associations is that of the CAG repeats and Stu I mutations, which are also associated with PCa independent of each other (4). One possible explanation is that the short alleles may impose higher transactivation on the receptor due to the inverse relation between the number of glutamine residues in the polyglutamine tract and associated transcriptional activity (5, 6). Men diagnosed at an older age appear to have longer CAG repeats suggesting that AR CAG repeat length may also be associated with PCa aggressiveness (7). However, conflicting information about association between variable length of CAG repeats and progression of PCa have been reported. Recently, some reports have indicated no correlation between the age of onset of the disease and number of CAG repeats (8). Similarly, there was no significant association was found between the length of CAG repeats and risk of PCa (9, 10). The conflicting data reported about association of CAG repeats in AR with the risk of developing the disease and aggressiveness may also have originated due to the differences in molecular sub types of PCa tumors chosen for the study, any tumor not predominantly driven by AR might not be influenced greatly by CAG repeats, however, CAG repeat length may be a determining factors for tumors responsive to androgenic regulation. Further

characterization of tumor sub-types of the subjects involved in study will provide more conclusive information on the association of CAG repeats and risks of PCa.

3.2. Ribonuclease 4 or 2'-5' oligoadenylate synthetase-dependent ribonuclease (RNase L)

RNase L is an interferon induced ribonuclease which degrades single-stranded viral and cellular RNAs and is important in antiproliferative and antiviral functions of IFNs (11)). RNase L has several functions such as viral RNA degradation, regulating mRNA stability, anti-cellular proliferation, and apoptosis, among many other functions (12). RNase L has been linked to hereditary PCa since the mid-1990s when it was included in the first linkage peak identified in a genome-wide scan of 91 high-risk families (13). RNase L stimulates the expression of genes which suppress PCa growth. In a recent study eleven SNPs were reported to account for genetic variation in RNase L (rs12034888, rs12757998, rs635261, rs12729828, rs10911099, rs627839, rs11807829, rs533259, rs627928, rs486907 and rs682585). In addition, a significantly increased risk of PCa with variant rs12757998 (A-G) was found (14). In AAs, rs12757998 (A-G) was associated with positive family history of PCa especially with high-grade disease compared to CAs (15). The genetic variation in RNAse L which is part of host immune system may indicate a potential alteration in association between inflammation prostate carcinogenesis tumor However, further association of RNase L with cancer disparity with respect to its function of RNA degradation, mRNA stability and anti-proliferation remained largely unexplored.

3.3. The macrophage scavenger receptor 1 (*MSR1*)

MRS1, which encodes the class A macrophage scavenger, is another gene that has been implicated in racial disparity in PCa. These are trimeric membrane glycoproteins (three different isoforms) which were first described in the deposition of cholesterol in arterial walls (16). *MRS1* binds to a variety of ligands including LDL and bacterial pathogens, and also mediates macrophage adhesion (17). Germ line mutations in *MSR1* have been linked to race specific prostate carcinogenesis (18). AAs appear to have increased frequency for *MSR1* Asp174Tyr mutation which has been associated with PCa. (19). Interestingly, Asp174Tyr missense mutation in *MSR1* is found about twice as frequently in AA PCa cases compared with controls, substantial allelic variations in MSR1 genes among different races have been reported, with Asp174Tyr found particularly in AAs, however clinical significance of this variation remained unclear (20).

Table 1. Genetics, microRNA, environmental factors, tumor microenvironment and epigenetic factors in PCa racial disparities. Factors listed by category along with their perceived effect in Pca

Variation	Effect	Race	Reference
Genetic variations			
Shorter AR CAG repeats	Increased Stu I mutations	AA	(3)
RNase L variant rs12757998	Associated with high-grade disease	AA	(10)
MSR1, Asp174Tyr missense mutation	Sporadic PCa	AA	(16)
CYP3A4	Altered testosterone metabolism	AA (46% homozygous)	(21)
CYP3A4*1B and CYP3A43*3	Diagnosis of PCa before age 60	AA	(22)
microRNAs			
Lower miR-152 expression	Lower DNA (cytosine-5)-methyltransferase 1 (DNMT1) expression	AA (50%)	(34)
2.2.5 fold increase in miR-26a	Downregulates EZH2 and wnt5a; increase in miR-26a shows increase in aggressiveness	AA	(28)
miR-1b-1, miR-30c, miR-301	expressed 3 times higher	AA	(29)
miR-151	Increased gain in AA men as a result of an SNP on 8q24	AA	(32)
miR-125b	SNPs in this region which disrupt BMPR1B expression	AA	(33)
SNP rs12940701 and rs200114569 in miR-152	Altered methylation of miR-152 promoter	AA	(34)
Environmental factors			
Increased fat	Increased PCa risk	AA, CA, Asian-Americans	(36)
Vitamin D deficiency	Higher incidence in PCa and higher mortality	AA	(39)
Tumor Microenvironment			
Microvessel density and macrophage	Increased concentration in tumors	AA	(42)
CDK2A(p16), CCNA2, CCNB1, CCNE2	Increased expression in tumor epithelium	AA	(42)
Autocrine mobility factor receptor, chemokine (C-X-C motif) receptor 4, and matrix metalloproteinase 9	Highly expressed in high-grade tumors	AA	(43)
Interferon-related DNA damage resistance signature (IRDS)	Linked to pro-metastatic EMT	AA	(44)
Extracellular matrix, integrin family and EMT pathways	Decreased activation in the stroma	AA	(41)
NCK2, ROCK2, Vinculin, PARVA, ACTN, ARP2/3, NID1, PPARD and TCF4	Up-regulated in stroma epithelium	CA	(41)
Epigenetic Events and Factors			
APC, RARB and NKX2.5.	Hypermethylated in tumors	AA	(51)
RARb2, SPARC, TIMP3, and NKX2–540	Hypermethylated in tumors	CA	(52)
NKX2–5 and TIMPC	Highly methylated in normal prostate	AA	(53)
CD44	Hypermethylated in tumors	AA	(54)

3.4. Androgen metabolism and CYP genetic variants

The Cytochromes (CYP) are involved in drug metabolism are another genetic factor which leads to racial disparities in PCa. CYP proteins contain heme as a cofactor and use a variety of molecules as substrates for enzymatic function (21). CYP proteins are the major enzymes involved in drug metabolism and many of these enzymes require a protein partner to deliver one or more electrons (22). Sequence polymorphisms in the CYP gene family members may influence PCa onset and outcomes, because of the role of these enzymes in the metabolism of a variety of substrates, including chemotherapeutic drugs (23). The CYP3A4 variant appears to be more common among AAs than CA men. This variant is involved in the metabolism of testosterone and an A→G transition in its promoter has been reported to exhibit ethnic variability, and is associated with a higher grade PCa in CA men (23, 24). Among AAs, 46% of men with PCa were homozygous for the CYP3A4 variant, whereas only 28% of AA healthy

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volunteers were homozygous. A positive correlation of association between CYP3A4 homozygous men and clinical characteristics in AAs has been reported. AA men homozygous for the CYP3A4 variant are more likely to present with higher grade of PCa (25). Additionally, in a pairwise interaction study between CYP3A4*1B and CYP3A43*3 allelic combinations indicated protective roles for early onset of PCa. Only 4% of CAs carry this allelic combination, while 35% of AAs reported to have this haplotype. Indicating that a subset of AAs who carry CYP3A4*1B and CYP3A43*3 combination are less likely to be diagnosed with early onset PCa compared to their CA counterparts, although this notion necessitates clinical validation (26).

3.5. Disparities in differential expression of regulatory microRNAs

miRNAs are small non-coding RNA molecules which also show racial disparities in several cancers, including PCa. miRNAs are conserved in plants, animals and some viruses and are an important evolutionarily component involved in post-transcriptional regulation of gene expression (27, 28). One miRNA can bind to many target messenger RNAs (mRNA) and control their translation or cause mRNA degradation (29–31). Differential expression analysis of miRNAs in 39 PCa tissues with matched controls (20 AAs and 19 CAs), showed that 50% of AA patients had statistically significant lower miR-152 expression compared to only 35% of CA patients (32). Another study showed a 2.2.5 fold increase for miR-26a in non-malignant, a 13.3. fold increase in malignant and 2.3.8 fold increase in metastatic tumors in AA compared to CA PCa samples of similar clinical stage and tumor grade (32). miRNA-1b-1, miRNA-26a and miRNA-30c-1, miRNA-219, and miRNA-301 were also found to be expressed differentially in PCa from AAs compared to those from CAs (33). Other miRNA that has been shown to be significantly downregulated in AAs when compared to CAs is miR-99b, this microRNA has also been related to development of more aggrieves PCa (34). However, differential expression could only provide an observational conclusion. Therefore, a deeper understanding of biological implications of these miRNAs in PCa progression and metastasis calls for further mechanism based studies to validate clinical observations.

3.6. Disparities of SNP's in miRNA regulation

Single nucleotide polymorphisms (SNPs) are the simplest form of DNA changes that occur at a frequency of about one in 1,000 base-pairs and are responsible for the diversity among individuals (35). SNPs in miRNA coding genes or seed regions are rare, nevertheless they appear to have an important gene regulatory implication. Several SNPs on chromosome 8q24 were identified and their presence was attributed

to overexpression of associated miRNAs. AA men shown increased expression of miR-151, present on 8q24, presumably as a result of a SNP in this region (36). SNPs that occur in miRNA seed regions are extremely rare, approximately 1%, and can significantly alter microRNA mediated gene regulation. Two SNPs in miR-125b are shown to disrupt the miR-125b binding site in BMPR1B (bone morphogenetic protein receptor type 1B) and differentially regulate the C and T alleles. (37). miR-152 expression is significantly decreased in AA patients when compared to CAs because of more than 30 SNPs which have been identified in this region. Interestingly, the loss of miR-152 expression and increase of *DNMT1* expression enhances the aggressiveness of prostate tumors (38). Two SNPs of importance, which alter the methylation status of miR-152, are rs12940701 and rs200114569. miR-152 appears to have significantly higher hypermethylated CpG islands than other miRNAs (38). In CAs these SNPs (rs12940701 and rs200114569) are less abundant therefore, lower methylation of this gene is natural when compared to AAs or Asians (38). Racial differences in SNPs in the seed region of many miRNA binding sites, could be detrimental in the regulation of carcinogenesis promoting target genes. SNPs in miRNA binding site may effect response to therapies and disease progression. Therefore, a thorough understanding of the differential expression of SNPs in AAs versus CAs could help predict their response to therapies for better prognosis (39).

4. DIET, OBESITY, AND METABOLISM RELATED DISPARITIES

Among environmental factors, diet especially fat consumption, is likely to play a part in the ethnic variations in PCa incidence. A positive association between fat intake and PCa risk in AAs, CAs, and Asian- Americans was shown (40). The data illustrates that AAs on average consumed more calories than CAs or Asian-Americans, and that a higher percentage of those calories are obtained from fat. Nevertheless, these caloric differences were only able to explain about 10% of the difference in incidence rates between AAs and CAs. Another contradictory finding indicates that diet induced obesity does not influence PCa tumorigenicity (41). However, *in-vivo* studies have affirmed the significance of differences in fatty acid intake and its association with tumor growth. Mice fed with omega-3 fatty acid reported reduced tumor volume and reduced expression of *IL-6, TNF*-α and *IL-10* compared to omega-6 fatty acid fed mice (42). These studies were also recapitulated in PCa xenograft model, where dietary fish oil and omega-3 fatty acid administration significantly reduced oncogenic *Bcl-2, BCLXL* and survivin expression resulting in a decrease in tumor growth (42). These findings indicate the beneficial effects of omega 3 fatty acids in clinical course of PCa. Race and culture have been linked

to differences in food selection and dietary intake, increased consumption of food high in fats increases the ratio of omega 6 to omega 3 fatty acids, which might be associated with higher incidences of PCa in AAs (43). Besides fatty acid intake, vitamin D, which is synthesized from sterol precursors has also been implicated in PCa (44). Vitamin D deficiency in AAs may partly explain PCa disparities, but the mechanism in which vitamin D impacts PCa pathogenesis and progression in AAs is not well studied.

5. DISPARITIES IN FACTORS INFLUENCING TUMOR MICROENVIRONMENT

Alterations in microenvironment of cells promote cancer initiation, which are further enhanced by the crosstalk between cancer cells and the preexisting modified microenvironment. The significance of constant evolution of the tumor microenvironment, leading to tumor formation, metastasis and refractoriness to therapy are getting increasingly clear (45). Numerous genes implicated in tumor microenvironment appear to be expressed differentially in AAs and CAs (46). Tumor microenvironment is largely influenced by the extent of angiogenesis and infiltration of immune cells, both of which monitor tumor cell proliferation. Studies indicate the differences in microvessel density, macrophage infiltration and expression of several cell cycle regulators such as *CDKN2A, CCNA2, CCNB1* and *CCNE2*. AAs are reported to have overexpression of *CDKN2A, CCNA2, CCNB1* and *CCNE2* in the tumor epithelium compared to CAs (47). Autocrine mobility factor receptor, chemokine (C-X-C motif) receptor 4, and matrix metalloproteinase 9, are also highly expressed in tumors of AAs compared to CAs (48). The disparities in tumor microenvironment also contribute to differences in therapeutic response. AAs exhibit a molecular signature that is almost identical with an interferon-related DNA damage resistance signature (IRDS) that predicts resistance to chemotherapy and radiation (43). IRDS has also been associated with pro-metastatic epithelial to mesenchymal transition (EMT) (49).

5.1. Stromal microenvironment in disparity

Normal and tumor tissues are maintained by stroma. The tumor stroma can change and promote growth, invasion, and metastasis (50). Racial disparity in stromal microenvironment has not been subjected to a systematic study, therefore not much is known about it comparatively in the PCa of CA or AA men. Recently, however, it has been documented some distinct cellular and molecular changes occur in the stromal environment surrounding tumors, also termed reactive stroma (51). Molecular change in the stromal microenvironment has been implicated in invasion and metastasis (52, 53). Normal human prostate is

composed of epithelial tissue and adjacent stroma. In PCa development the stromal environment changes morphology and can acquire mutations, which increases proliferation and malignant properties of the cancer cell (53). Several genes associated with the tumor-adjacent stroma are expressed differentially in different races such as AAs and European/Caucasian-Americans (EA). The extracellular matrix, integrin gene family and signaling mediators of EMT pathways are downregulated in the stroma of AAs (46). Recent study indicates that 56 tumor-associated and 677 stroma-associated genes were differentially expressed in AAs and CAs, majority of these included the proteins required for cell adhesion such as *NCK2, ROCK2, Vinculin, PARVA, ACTN, ARP2/3, NID1, PPARD* and *TCF4*, which were upregulated in the stroma of CA and downregulated in AAs (46). The downregulation of genes involved in the stability of cell adhesion in AAs, and differential expression of genes influencing the tumor stroma (listed above) in CAs versus AAs could be a reason that AAs experience an aggressive form of PCa, hence deserve further investigations.

6. EPIGENETICS AS RACIAL DISPARITY

Epigenetics plays an important role in the expression of genes and can occur differentially among races. A common earlier epigenetic event in PCa is hypermethylation of CpG islands in promoter regions. Several promoters of PCa associated genes which are hypermethylated in localized PCa include *GSTP1, APC, RASSF1a, COX2,* and *MDR1 (48)*. In addition, *ER-a, hMLH1,* and *p14/INK4a* are known hypermethylated genes in metastatic disease, suggesting a distinct epigenetic signature followed in disease progression (54). Extensive comparative analyses of epigenetic changes between men of Caucasian and African ancestry have not been undertaken. However, limited data show that AAs appear to have higher methylation of key genes such as *APC, RARB* and *NKX2.5.* when compared to CAs (55). Although, methylation of *GSTP1* occurs early in PCa, this gene wasn't significantly differentially methylated when comparing AAs and CAs. On the other hand *RARβ2, SPARC, TIMP3,* and *NKX2–540* were hypermethylated in AA with PCa as compared to CA (56). Interestingly, several genes such as *NKX2–5* and *TIMPC* were shown to be highly methylated in the normal prostate of AAs when compared to CAs with *NKX2–5* showing increased methylation in AAs as the men got older (57). CD44, which codes for an adhesion and signal transduction membrane protein was also shown to be hypermethylated in AAs. Interestingly, except the racial difference no other reason was identified for such progressive escalation of methylation within the AA population (58). Detailed analysis is needed to characterize the disparity in epigenetics in CA and AAs with PCa.

7. CONCLUSIONS

Studies focused on genetic variations and underlying molecular mechanisms influencing racial disparity are yet not well defined, therefore need special consideration. Increased understanding of the race-specific differences in disease progression is essential to distinguish between genetic and environmental factors, which can facilitate better identification of therapeutic targets and prognostic markers for a specific population. In this report, we attempted to summarize the association between the unique signature of mutations in RNase L, CAG repeat length, *MSR1* gene and CYP-450 3A4 in AAs and significantly higher risk of PCa. In addition to the PCa susceptibility genes, several miRNAs, such as miR-152 and miR-26a are also differentially expressed and lead to an increase in aggressiveness of PCa in AAs. These genetic alterations, metabolic differences and dietary intake appears to promote differential modifications in tumor microenvironment, as indicated by highly expressed cell cycle regulators and metalloproteases in the epithelium of AAs. Genetic differences in the tumor microenvironment also contributes to unique interferon-response gene pattern, which determines the disparity in response to radiation and chemotherapy. Last but not least, epigenetic changes also a cause of racial disparity as reflected by higher methylation of few key genes such as *TIMP3, APC, RARB* and *NKX2.5.* in AAs.

8. FUTURE PERSPECTIVE

Comparing race specific incidences and their association with genetic, epigenetic, and environmental components provides a better scope for understanding of the heterogeneity observed in PCa progression and refractoriness to therapies. Meta-analysis of genome wide data and epidemiological studies identifying the differences in environmental factors of different races are required to understand molecular and cellular mechanism behind the race-specific PCa growth. Such analyses can also help pinpoint future specific research area for better diagnosis and an increased likelihood of identifying better therapeutic options, therefore ensuring positive outcomes. There is a strong need for future clinical, scientific and socio-cultural research involving a multidisciplinary approach to identify and adjust the modifiable risk factors and introduce targeted interventions for the AA population.

9. ACKNOWLEDGEMENTS

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Send correspondence to: Girish C. Shukla, 2121 Euclid Ave, Cleveland OH, 44115, Tel: 216-687-7422, E-mail: g.shukla@csuohio.edu