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Opportunistic Virus BKV: Racial Disparities in Prostate Cancer

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Abstract

Prostate cancer (PCa) is the most common malignancy and the second most leading cause of cancer death among men in the United States. More specifically, African American (AA) men are at 1.6 times higher risk of being diagnosed and 2 times higher risk of death from PCa, compared to European-American (EA) men or other ethnicities. BKV is an emerging opportunistic pathogen that infects 90% of the human population and is known to reactivate in immune-compromised hosts and has been implicated as a cofactor in early stages of PCa. Reactivated BKV may be a more virulent strain that emerges in the absence of host immune response. Therefore, it is plausible that BKV genetic diversity within immune-compromised cancer hosts may allow more virulent strains to reactivate to opportunistically cause disease.BKV replication is orchestrated by a regulatory protein large T antigen (LTag) which binds products of tumor suppressor genes (pRb family, p53) and interferes with the strategic checkpoints of the cell cycle of infected cells, thereby resulting in transformation and cancer progression. The association of viruses and their evolutionary dynamics in human disease is critical for advancement in tumor biology therapeutics and clinical diagnoses. This review article describes to better understand racially derived differences in PCa and a potential role for BKV as a cofactor in PCa progression.

Abbreviations: BKV: BK polyomavirus; PCa: Prostate cancer; JCV: JC virus; SV40: Simian Virus 40; CMV: Cytomegalovirus; HSV: Herpes Simplex Virus; HHV: Human Herpes Virus; HPV: Human Pappilloma virus; EBV: Epstein Barr Virus; XMRV: Xenotropic murine leukemia virus-related virus; TAg: Major T antigen; tAg: Minor T antigen; NCCR: non-coding control region; CRPC: Castration Resistant Prostate Cancer; SEER: Surveillance, Epidemiology and End Results Program; PCA3: Prostate Cancer gene 3; PIA: Proliferative Inflammatory Atrophy PIN: Prostatic Intraepithelial Neoplasia; BPH: Benign Hyperplasia; TMPRSS2-ERG: Transmembrane protease, serine 2; MALAT-1: Metastasis-associated lung adenocarcinoma transcript-1; HI: Hemagglutination-inhibition; IF: indirect immunofluorescence RIA: radioimmunoassay; ELISA: enzyme-linked immunoassay

Introduction to BKV

BK polyomavirus (BKPyV) is a small circular, double-stranded (~5kb), non-enveloped virus with an icosahedral capsid and a member of the Betapolyomavirus genus in the Polyomaviridae family [1]. It was isolated from the urine of a Sudanese kidney transplant recipient with ureteric stenosis, with initials BK [2]. Other common polyomaviruses that affect humans include JC virus (JCV), Simian virus 40 (SV40), and Merckle cell virus, to name a few. While BKV and JCV are ubiquitous in humans, SV40 is believed to be introduced in the human population by contaminated polio vaccines produced in SV 40- infected monkey cells. The DNA sequence identity shared between BKV and JCV is 72%, while 69% between BKV and SV40 and 68% between JCV and SV40 [3]. It has been suggested that BKV co-evolved with humans and remains latent in healthy individuals for most of their lives. Studies have reported that 90% of the human population is infected with BKV. Typically, 10-30% infants and 65-90% individuals become infected with BKV at a young age (~5-10 years old), however, the virus remains asymptomatic or mildly symptomatic in immunocompetent individuals and persists in the kidney, peripheral-blood leukocytes, and the brain [4-6].

BKV Pathogenesis

BKV has been implicated in multiple diseases such as hemorrhagic cystitis, ureteric stenosis, vasculopathy, pneumonitis, encephalitis, retinitis, autoimmune diseases, and cancer [1]. However, due to the lack of many studies in understanding the role

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and mechanism of BKV replication, the exact role of BKV in these diseases is still obscure. Unlike most common viruses, information on BKV diversity is limited and the understanding of its evolution and variability is based on analogous studies of other viruses such as HIV, HPV or SV40. In 2012, the International Agency for Research on Cancer, a part of the World Health Organization, classified BK polyomavirus as a group 2B- "potentially carcinogenic to humans" [7].

The detection of BKV, JCV and SV40 sequences have been found in peripheral blood mononuclear cells (PBMC), suggesting a possible route of entry for the virus to spread to other tissues of the infected host [8&9]. In case of BKV, the transmission routes are not fully recognized, and it is assumed that the infection is transmitted via the respiratory tract, fecal-oral tract, blood, or through organ transplant [10]. The most common high throughput techniques, such as quantitative real-time PCR, DNA Microarray, Fluorescent in situ hybridization (FISH) have been employed in determining BKV DNA detection in tissues of cancer patients. Out of these, qRT-PCR remains the best gene assay method for BKV DNA detection in tissues. Other methods such as Hemagglutination-inhibition (HI), complement fixation, indirect immunofluorescence (IIF), RIA, ELISA, and western blot are also widely employed assays [11]. Therefore, while the sensitivity of each test may vary, the modalities of virus transmission in humans are still presently not clear. Although the virus is known to infect many different cell types, the renal tubular and urinary tract epithelium are most commonly infected. Upon reactivation, the immune system controls the replication of BKV and allows it to remain latent. During immunosuppression, the virus enters its lytic phase in kidney cells, which results in detachment from the basement membrane, and the cells get infected with the virus that may appear in urine as decoy cells, leading to viruria.

Subsequently, the virions can egress capillaries, causing viremia. All these events can result in necrosis and lytic destruction of the renal epithelium layer followed by inflammation, a common occurrence in kidney transplant recipients or in hemorrhagic cystitis [4].

BKV DNA has been detected in brain tumors, neuroblastoma, bone, insulinoma, prostate and Kaposi sarcoma [8,12-14]. Flagstead et al. [15] confirmed the presence of BKV in brain cancers via PCR that detected the DNA in 17 out of 18 patients with neuroblastoma along with T-Ag expression in them. Arthur et al. [16] refuted the study indicating a lack of association of BKV DNA to brain cancers. BKV DNA has also been detected in high-grade squamous intraepithelial cervical lesions [17]. In addition, the risk for invasive bladder cancer in kidney transplant recipients and prostate cancer is strongly correlated with BKV infection [18-23]. Several studies have reported the manifestation of kidney or bladder cancer due to BKV infection- related nephropathy. Narayanan et al, [24] confirmed the presence of BK virus in kidney transplantation and cancer, although no infection in the donor's healthy kidney was found. Similarly, Geetha et al. [25] reported the presence of BKV DNA in a patient with bladder cancer and BKV nephropathy, confirming the role of the virus as a causal transforming agent confirmed via the differential expression of BKV large T antigen in the malignant cells except for stromal cells or nondysplastic urothelium.

Limited studies have also reported the role of BKV, JCV and SV40 prevalence in colorectal cancer [26&27]. Drop et al. [28] reported a significant correlation among different viruses upon co-infection such as HPV, EBV and BKV in polish patients with oral, oropharyngeal, and laryngeal squamous cell carcinomas. Several studies have reported a connection between BKV and the oral cavity [29-31]. Jeffers and Cyriaque [31] suggested a role of BKV transmission via the oral route as it was reported in HIV-SGD (salivary gland disease).

BKV Structure and Genome

The site of entry, mechanism of dissemination and mode of transmission modulating BKV infection mechanisms are still not clearly known. It has been reported that the initial binding of capsid protein to host cellular receptors such as N-linked glycoprotein with 2,3- linked sialic acids and ganglioside receptors Gt1b and GD1b; initiates the entry of the virus into the host [32]. Subsequently, the virus gains entry into the host cell via caveolin- dependent endocytosis [33]. Once delivered to the endoplasmic reticulum (ER), the capsid disassembly initiates [34,35]. The translocation from ER into the host cell cytosol and finally, to the nucleus is orchestrated by the nuclear localization signal (NLS) domains within the capsid minor structural proteins and the host nuclear pore complex components, thereby facilitating its nuclear import [36], wherein the cell transcription machinery initiates viral gene expression [37]. Upon viral replication initiation, the late genes are transcribed from the opposite strand in an opposite direction from the early genes. The translocation of capsid proteins after being synthesized in the cytoplasm is followed by their assembly with the viral genome into the virion particles in the nucleus. The viral genome is also packed with histones H2A, H2B, H3 and H4. Virions are finally released by lysis-dependent/ independent mechanisms. In case of abortive infections, the viral genome is integrated into the host cells as an episome and remains latent [38].

The polyomavirus genome organization consists of three functional regions: the non- coding control region (NCCR) and two coding regions: early and late. The non-coding region is the site of replication origin (ORI) and transcription. The NCCR/TCR of the proposed archetypal BK strain WW is divided arbitrarily into five transcription factor binding sequence blocks, called O (142 bp), P (68 base-pairs), Q (39 base- pairs), R (63 base-pairs), and S (63 base-pairs). These binding sites entail the promoter/enhancer sequences. The early and late region code for proteins, two and four, respectively. The early proteins include the large tumor antigen (TAg), the small tumor antigen (tAg), and the recently discovered truncated tumor antigen (TruncTAg). The regulatory protein large tumor antigen (LTag), coded by the early protein, is primarily associated with BKV replication [39]. Expression of the large T antigen immortalizes human cells in culture, transforms rodent cells in culture, and induces tumors in transgenic mice. The Dna J domain in the N-terminal part of LTAg as well as the ATPase/

helicase activity, are necessary for efficient viral DNA replication. LTAg of most polyomaviruses binds repeats of the 5'-GRGGC-3' motif. In higher quantities, the accumulation of LTag protein initiates DNA replication in the cell nucleus via DNA polymerase to the viral origin of replication, thereby shutting off early gene transcription and regulating expression of late proteins. This results in lysis of cells, eliciting an antibody response to VP1 in most healthy individuals. In the case of abortive infection, uncoupling of LTag from VP1 induces an oncogenic response, by binding to the products of tumor suppressor genes (pRb family, p53) and inactivating by sequestration in the cytoplasm, thus obstructing the strategic cell cycle checkpoints of infected cell and causing transformation and tumor progression. The late region codes for the capsid proteins, that facilitate the virion assembly. It consists of three capsid proteins (VP1, VP2, VP3) and agnoprotein. The capsid consists of 72 copies of homomeric VP1 pentamers cross-linked by intermolecular disulfide bonds to form a T=7d icosahedron structure [40]. The role of LTag and VP1 have been identified as therapeutic markers against anti-polyomavirus agents [38].

Based on the NCCR sequences, BKV can be classified into two main groups: the archetype and the rearranged. The archetype group is commonly found among healthy individuals and is difficult to culture in vitro, whereas the rearranged BKV is associated with diseases and can be easily propagated using cell culture methods. In addition, based on genetic heterogeneity in the VP1 sequence, there are four types of BKV viruses: Subtype I is most distributed worldwide (80%), followed by subtype IV (15%) that is prevalent in Asia and parts of Europe, while subtypes II and III are sister groups that are rarely detected [41-44]. [45] identified a 100 bp-region of the VP1 gene using phylogenetic algorithms for identification of the various BKV subtypes and classified it as the BK typing and grouping region (BKTGR). Another BKV variant, BKV-IR, was detected using Southern blot hybridization in human insulinoma [46]. The genome of BKV-IR contains an IS-like structure, a type of stem-loop transposable element that can integrate and excise from the host genome, thus promoting cell transformation by excision from viral DNA and insertion in the cell genome, functioning as a mutagen. However, the study failed to show the integrated viral sequences in the human tumor from which it was isolated although BKV-IR was able to infect monkey and human cells, transform rodent cells and induce tumors in hamsters. Therefore, more comprehensive research focusing on comparable analysis to determine the prevalence of different strains worldwide should delve into the viral oncogenic potential leading to progression of tumors. (Figure 1).

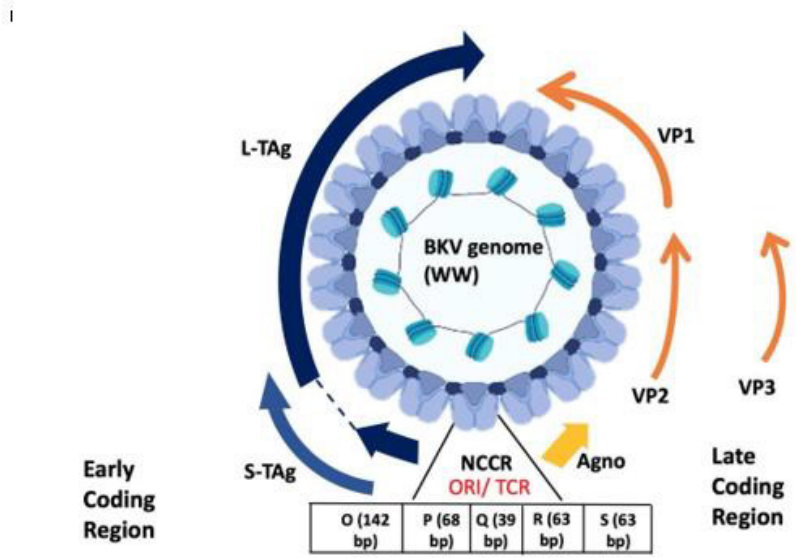

Figure 1: Organization of the Archetypal BKV Genome (WW). The gene products encoded by the early region (large T-antigen and small t-antigen) and the late region (the agnoprotein, and the capsid proteins VP1, VP2, and VP3) are indicated. The non-coding control region (NCCR), consisting of the origin of replication (ORI), early and late promoter/ enhancer sequences represented by the O-P-Q-R-S nomenclature is shown.

Prostate cancer and racial disparities

Prostate cancer (PCa) is the most common malignancy and the second leading cause of death among men in the United States [47]. The greatest incidence is witnessed in more developed countries such as North America, Western and Northern Europe, Australia, and New Zealand and in parts of the Caribbean and sub- Saharan Africa (Figure 2). Race/ethnicity is a crucial factor in the mortality rates of prostate cancer representing one of the largest cancer disparities within the US. The incidence of prostate cancer as well as mortality rate in African American (AA) men is higher as compared to Caucasian (CA) or European (EA) and Asian-American men. More specifically, AA men are at 1.6 times higher risk of being

diagnosed and 2 times higher risk of death from PCa compared to Americans of European ancestries. Most African - American men are diagnosed at a younger age, with higher tumor grade and volume at surgery and with a greater potential for metastasis [48]. Overall, The Cancer Genome Atlas (TGCA) cohort indicates AAs have a lower median age at diagnosis with an average Gleason score of 8. According to the Surveillance Epidemiology and End Results Program (SEER) Statistics data, the five- year relative survival rate was 99.6% for European men and 95.9% for African- American men. The age-adjusted PCa mortality rate was also found to be two to three-fold higher in African- American men, compared to European men or men of other ethnicities (Figure 2-4). Both non-/ biological risk factors such as lack of access to care, diet, age, lifestyle, family history, hormones, socio-economic status have been implicated as causal factors to the difference in racial disparities of PCa incidence [48,49]. Moreover, the major challenges in different treatment regimens result in diminished survival rates following treatment in AA men as opposed to EA men. Besides socio-economic reasons, phenotypic and genomic heterogeneity can be attributed to racial disparity differences in tumor etiology [50], such as genetic polymorphism, gene mutations, epigenetic modifications, and miRNA alterations [49].

Prostate specific antigen (PSA) levels in serum of the patient serve as the most reliable physiological/pathological diagnostic indicator of PCa [48]. US Preventive Task Force (USPTF) reported a correlation between PSA screening linked to the potential benefit of decreasing the number of deaths in men with PCa aged 55-69, however the data for men from all races over 70 is less convincing [51]. Notably, significantly higher PSA levels were seen in African - American men, with or without prostate cancer when compared to European-American counterparts [52–54]. Another parameter in the diagnosis of PCa is the biomarker Prostate Cancer gene 3(PCA3); which is a non-coding mRNA detected in the urine of patients [55]. A strong indication of PCa is commonly depicted through higher ratios of PCA3 mRNA to PSA mRNA (PCA3/PSA). However, PCA3 is not solely a reliable predictor for prognosis in PCa patients as opposed to PSA. An androgen-regulated Transmembrane protease, serine 2 (TMPRSS2-ERG) fusion gene has also been found to be a promising urinary biomarker test; considered to be highly PCa specific [56,57]. In addition, certain DNA methylation biomarkers for PCa have also been reported. Although biomarker sensitivity and specificity play a crucial role in the initial diagnosis of PCa and have revolutionized the epidemiology and prognosis of PCa, additional investigation for more accurate specificity of other biomarkers is required (Figure 2,3) [58&59] Table 1.

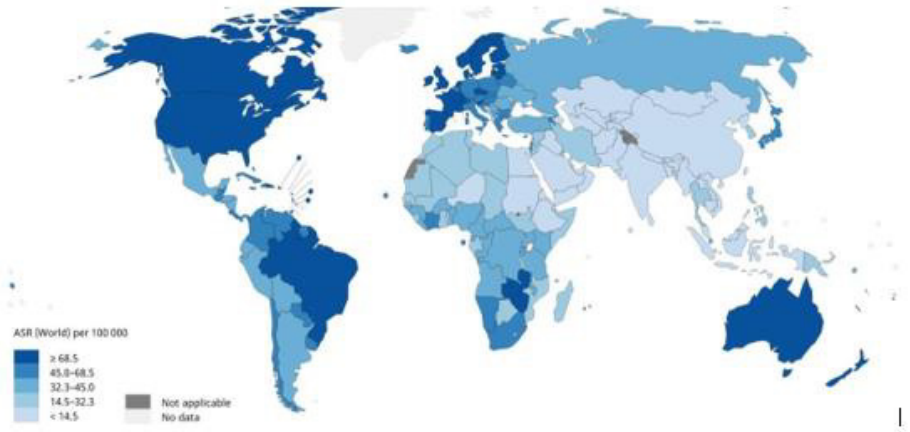

Figure 2: Map showing estimated age-standardized incidence rates for prostate cancer worldwide in 2020, in males including all ages. Created with mapchart.net. Data obtained from Globocan 2020 [58].

Table 1: Estimated Number of Incident Cases for Prostate Cancer, Males, All Ages [58].

Population	Number	Uncertainty interval	Crud e Rate*	ASR (World)*	Cum. risk**
Asia	3349988	[3263240.0-3439050.0]	141.2	123.3	31.19
Europe	108425	[1045780.0-1123670.0]	299.7	140	36.54
Northern America	367856	[366263.0-369456.0]	201.5	98.9	29.15
Latin America and the Caribbean	365135	[349533.0-381433.0]	113.5	98.1	28.93
Africa	323883	[258540.0-405740.0]	48.3	90.4	24.73
Oceania	37923	[34864.6-41249.7]	177.5	106.2	33.24

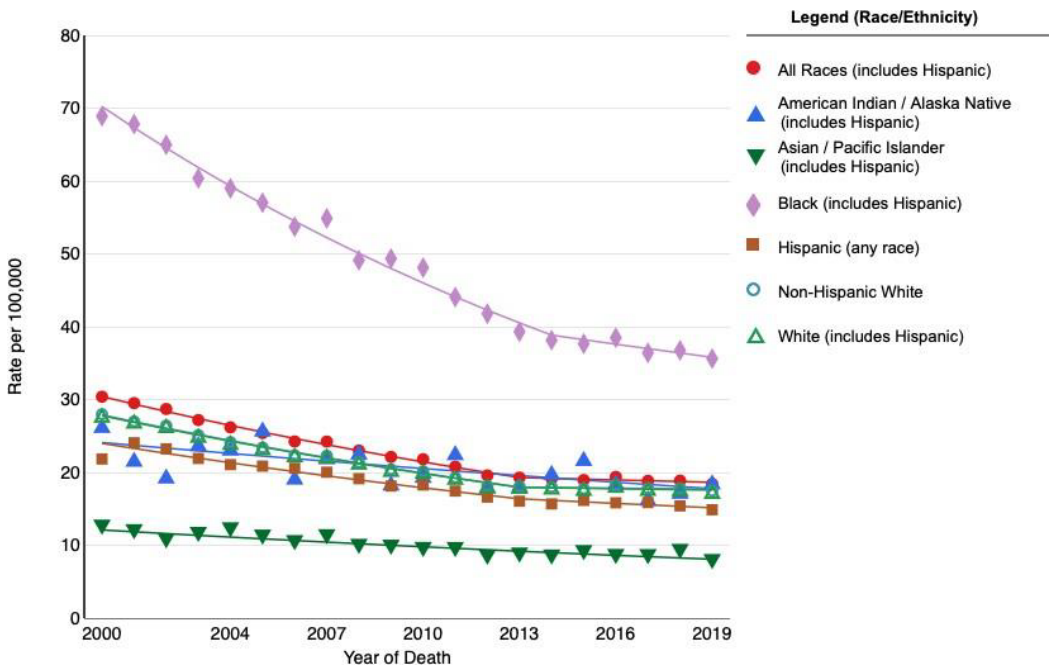

Figure 3: Recent Trends in U.S. Age-Adjusted Mortality Rates, 2000-2019 Male by Race/Ethnicity, All Ages, Data source: US Mortality Files, National Center for Health Statistics, CDC [59].

Racial genetic susceptibility differences in PCa

Gene polymorphisms

The most prevalent alterations in prostate cancer genomes are fusions of androgen- regulated promoters with ERG and ETS family of transcription factors. 40-50% of prostate tumor foci translating to over 100,000 cases annually in the US amounts to TMPRSS2-ERG fusion type of molecular alteration [60,61]. Besides these, the most frequently mutated genes in primary prostate cancers are SPOP, TP53, FOXA1, and PTEN [62]. Among the several different subtypes of PCa reported, ERG subtype was found to be lower (27.3%) while the SPOP subtype was more (22.7%) prevalent among AA subpopulation than EAs. The common chromosome 8q24 variants associated with increased prostate cancer risk, has been found to be increased in African – American men [63-65]. Other genetic variations suppressing tumors such as EphB2 [66] or regulating cell apoptosis such as BCL2 [67] are found to be significantly higher in AA men. These genetic variations manifest a more aggressive form of the disease in AA men, although external factors such as disparities in lack of adequate screening and access to healthcare cannot be neglected.

Genomic and transcriptomic dysregulation such as SPOP mutations, TMPRSS2-ERG fusions, PTEN deletions/losses, immune signaling, and expression of non-coding RNAs have been reported to be significantly different in AA men than EA men [68]. Genome-wide association studies (GWAS) have identified novel susceptibility loci in African men [64,69,70]. Jaratlerdsiri et al. [71] reported the use of deep whole genome sequencing (WGS) for profiling genomic variation in somatic variants in men with PCa from Africa, particularly South Africa and found an overall 1.8-fold increase in somatic variants in African tumors as opposed to those of European ancestry, although genomic rearrangements were found to be less frequent. Other genomic rearrangements reported in African men were in accordance with those reported in African - American men. Androgen receptor (AR) is an intracellular hormone receptor and a transcription factor and the androgen receptor (AR) signaling is a critical parameter in PCa pathogenesis [72]. Exon encoding amino-terminal transcriptional domain of AR consists of two polymorphic repeats of high frequency, CAG and GGN. The length of CAG repeats is reported to be different in AA (average 19-20) and EA (average 21-22) races. Additionally, CAG repeats polymorphism has been found higher in AA men, increasing the risk of PCa in them [73&74].

p53 polymorphisms

The transcription factor p53, encoded by TP53 gene, is also known as the guardian of the genome and plays a major role in regulation of the cell cycle, DNA repair, apoptosis and as a tumor suppressor [75]. Somatic mutations in p53 have been suggested in ~50% of cancers although relatively low in PCa (76,77). Missense mutations are the most common type of mutations reported for p53 in cancers. In the TGCA cohort, a whole genome sequencing of 333 samples from men with localized prostate cancer detected a mutation rate of 8% in TP53 [78]. Whereas, in castration-naïve metastatic prostate cancer, TP53 mutations were found to be significantly higher ranging between 28% to 36% than those in primary prostate cancer but lower than those found in Castration-resistant prostate cancer (CRPC) [79-81]. Therefore, the marked differences in TP53 across different grades of prostate cancer indicate towards the immunological target mutant p53 [82]. However, cytoplasmic localization of p53 and wild type

nuclear localization signal/sequence (NLS) have been reported in association with BKV LTag in PCa, rendering the possibility of mutant p53 as an immunological target [20&22]. Cytosolic p53 expression has been shown to be associated with poor outcome and progression to CRPC (83). A study demonstrated that combined therapy of Pmp53 (a plasmid harboring both mdm2 siRNA (Si-MDM2) and the wtp53) with zinc inhibited tumor growth in mouse xenograft models, while retaining wild-type p53 conformation, thereby enhancing the downstream transcriptional regulation of p21 and bax gene expression. The in-vivo findings in this study were supplemented with an in vitro culture of PCa cell lines analysis, showing a similar positive effect on cell cycle arrest and apoptosis [84]. Another study demonstrated restoration of the native p53 function in PCa by knockdown of G3BP2, an AR target gene that associates with SUMO E3 ligase RanBP2 and promotes p53 nuclear export, thus increasing p53 nuclear accumulation and reduced tumor growth in-vivo, indicative of G3BP2 as a plausible therapeutic target to restore native p53 function in PCa [83]. Moreover, while Suzuki et al. [85] reported that the Pro/Pro genotype of p53 codon72 was associated with a risk of PCa only in patients with a family history of Japanese population. A meta-analysis suggested a weak association of p53 codon Pro72Arg polymorphism with prostate cancer risk [86].

As for racial differences owing to p53 polymorphisms, population- dependent allele frequencies have been found to be less prevalent in Europeans compared to Africans with respect to p53 P72R SNP and Pro (C allele). The p53 Pro allele role has been indicated to be significantly variable in some major ethnic groups such as Caucasians and Taiwanese populations, whereas a contributing risk factor in men of African descent. Ricks-Santi et al. [87] in a case-controlled study demonstrated a marginal prevalence with respect to p53 Pro72Arg SNP polymorphism, the G allele coding for Arg allele associated with the prevalence of PCa in men of African - American descent.

Differential expression of miRNAs in PCa

MicroRNAs (miRNAs) are small, non-coding, 19-25 nts in length RNA that regulate gene expression post-transcriptionally. They do so either by degradation of target mRNA or inhibiting translation by complementarity targeting mRNA [88]. Differential expression of miRNAs has been reported in prostate cancer. Calin and Croce, [89] reported five miRNAs differentially expressed in prostate tumors among AA and EA populations, which are, miR- 301, miR-219, miR-26a, miR-1b-1 and miR-30c-1. These were at least three times differentially expressed in AA vs EA origins. Theodore et al. [90], also investigated the expression of miR-26a in non-malignant, malignant, and metastatic PCa cell lines of AA and EA populations. They reported increased (2.2 to 3.3 folds) expression of miR-26a in AA prostate cancer cells as compared to EA, examined under similar clinical stage and grade of tumor. However, an increase in miR-26a expression levels in more aggressive prostate cancer cells of both AA and EA origins was also seen. Later, the same group observed significantly lower expression levels of another miRNA; miR-152 in AA populations as compared to EA patients. The ectopic expression of miR-152 in PCa cell lines down- regulated DNA (cytosine-5)-methyltransferase 1 (DNMT1) through direct binding in the 3'UTR. Thus, leading to a possible conclusion that miR-152/DNMT1 may contribute to tumor aggressiveness, specifically in AA PCa patients [91]. Wang et al. [92] identified 22 miRNA signatures in AA and 18 in EA populations. They also reported novel AA-specific enriched miRNA- mRNA pairs critical in driving oncogenesis, including miR-133a/MCL1, miR-513c/STAT1, miR-96/FOXO3A, miR-145/ITPR2, and miR-34a/PPP2R2A. These deregulated miRNA-mRNA pairs targeted the EGFR-PI3K-AKT signaling, driving PCa aggressiveness in the AA populations. Therefore, the use of miRNAs can serve as potential therapeutic targets for PCa treatment and unravel the underlying mechanisms associated with racial heterogeneity in tumor aggressiveness.

Overexpression of LncRNAs in PCa progression

Besides miRNA, long non-coding RNAs (lncRNA) as the name suggests are long non-coding RNAs (>200 nts in length) have been reported to be overexpressed in PCa [93]. Lnc- SNHG17, was found to be highly expressed in castration resistant prostate cancer (CRPC), serving as a competing endogenous RNA (ceRNA), inhibiting miR-144, which in turn, upregulated CD51, amplifying CRPC cell proliferation and invasion [94]. Another lncRNA, LncRNA HOXD-AS1 promotes castration via WDR5 mediated histone 3 lysine 4 tri- methylation and regulation of other downstream genes, such as PLK 1, AURKA and CDC25C [95]. Two LncRNAs; Lnc- HOTAIR and Lnc- LBCS, have been reported to interact with the AR and result in CRPC progression. The former prevents the ubiquitination and degradation of the AR while the latter inhibits translation of the AR mRNA via interaction with hnRNPK [96].

Metastasis-associated lung adenocarcinoma transcript-1 (MALAT-1), approximately 8000 nt long non-coding RNA, originally overexpressed in non-small cell lung cancer metastasis, has been suggested to play a role in CRPC progression both in vivo and in vitro. Silencing of MALAT1 was further reported to inhibit CRPC cell proliferation by arresting the CRPC cell in the G0/G1 cycle, corroborating its role in PCa progression, aggression, and proliferation of prostate cancer cells [97]. In addition, MALAT-1 knockdown was shown to inhibit proliferation and migration, facilitating apoptosis by upregulating the expression of miR-1 (a tumor suppressor miRNA reported to be downregulated in PC tissues and cells) and downregulating KRAS (a target of miR-1) in androgen–receptor negative PCa cells [98]. Thus, these studies established the role of MALAT-1 as a potential/ therapeutic target for suppressing castration- resistant PCa. Moreover, Jeffers et al. [99] found a substantial upregulation of MALAT-1 in the presence of both polyoma (BKV) and papilloma (HPV) oncoproteins, which disrupt p53 expression. Thus, considering MALAT-1 as a biomarker for p53 deregulation and therapeutic target for PCa, it can be hypothesized that BKV- mediated upregulation of MALAT-1 may play a role in PCa progression.

BKV: a cofactor in etiology of prostate cancer

Viruses, as infectious agents have an association with ~20% of human cancers worldwide. Viral infections could act as cofactors in etiology of prostate cancer progression. Many viruses are known

to interact with host proteins and induce changes in their genetic, immunological and inflammatory pathways leading to initiation or progression of tumors [100]. Viral products, such as, Large T antigen of polyomaviruses, or E6/E7 proteins of HPV, can transform PCa cells and interfere with the interferon (IFN) signaling pathways [101]. The complexities of host genetics additionally favor or impede control of viral infections, enabling the virus to exert its cytopathic effects and transform normal prostate cells. A detailed literature of host genetics and viral infection interplay in prostate carcinogenesis is reviewed in [102].

Viruses such as the human papillomavirus (HPV), herpesviruses including cytomegalovirus (CMV), human herpes simplex virus type 2 (HSV2), human herpesvirus type 8 (HHV8) and Epstein-Barr virus (EBV), and xenotropic murine leukemia related virus (XMRV), have been found in the prostate. However, a direct association of these viruses with prostate tumorigenesis has not yet been established [103]. Not much evidence has indicated the role of viral infections in the etiology of PCa, possibly due to small sample size, inability to test non-persistent infections and inadequate tissue sampling or sensitivity of current viral detection methods [103]. Briefly, a link between HPV and Mediterranean and Asian population for HPV subtypes 16 and 18 with PCa was reported [104-106]. In addition, a Finnish cohort study demonstrated the seropositivity for HPV-18 and HPV-16 associated with PCa [107&108]. However, a meta-analysis showed a weak association between HPV-16 and PCa but not for HPV-18 [109]. CMV, HSV-1, HSV-2, HHV-8 and EBV infections have also been investigated in PCa, although a significant association between these sexually transmitted pathogens and PCa has not been established [110]. RNASEL/HPC, a candidate gene for PCa, also involved in antiviral and antiproliferative role of IFNs and its variant R462Q is also known to affect the suppression of viral infection, as reported for XMRV in PCa [100]. Two proteins of HPV; E6 and E7 are known to interact with p53 and pRb respectively resulting in their degradation or inactivation [111]. Increased titer of antibody to L-Tag was found to be associated with an increase in expression of IL-10 as opposed to IFN- γ in patients with PCa and benign prostate hyperplasia.

BKV has been reported to cause proliferative inflammatory atrophy (PIA) and prostatic intraepithelial neoplasia (PIN) in early- stages of prostate cancer. High frequency of BKV and JC virus DNA have been reported in prostate cancer patients. Delbue et al. [21] reported BKV prevalence of 16.5% (95% CI 13.8%-19.2%) among the tissues from PCa patients, and 7.0% among the control tissues from Benign Hyperplasia (BPH) patients (95% CI 5.2%-8.8%; $p<0.0001$). Highest BKV infection rates of about 28% in PCa and 15% in BPH samples were also reported in a study from Iran [112]. Among the spectrum of human cancers, prostate tumors have a relatively low frequency of mutations with respect to p53 and RBI genes, however, the presence of oncoproteins LTag and small antigen in polyomaviruses are capable of transformation of normal cells (19,20). A case-controlled study among cancerous prostate cancer patients in Sudan detected higher frequency of BKV LTag as compared to patients with BPH prostates. The study also showed aging and geographical affiliation as important cofactors in progression of PCa [22]. BKV infection in different cell types was shown to upregulate genes associated with cell proliferation and IFN-signaling pathway, indicating the possible dissemination of the virus to various sites and lodge a persistent infection [113]. Elevated levels of CXCL10 and ZBP1, released by leukocytes in response to BKV infection has also been reported, facilitating BKV's ability to trigger an innate immune response [114]. The mechanistic basis of the viral-host interaction was not explained in these studies and thus needs more insight. Due to the high prevalence and frequent reactivation of BKV, it has been difficult to define its role in cancer and is still considered controversial. Until now, the exact underlying molecular mechanism orchestrating the viral oncogenic activity in the tumor microenvironment is not known.

Additionally, a comparative analysis among racial profiles of men with PCa and a causative link with the prevalence of BKV in them has not been demonstrated so far. A thorough investigation of comparable analysis for viral infections driving tumor evolution and associated heterogeneity between racial groups would be interesting to look at. Therefore, underpinning the genomic signatures/biomarkers determining racial disparities within a particular geographical location should advance our understanding of the virus oncogenic potential.

Thus far, the only plausible explanation for BKV's co-factorial role in PCa progression has been explained by the 'hit and run hypotheses. Reeves and Dong [115&116] explained it as the binding of a viral antigen to a self/autoantigen; triggers an immune response that subsequently can be perpetuated by self-antigen. In other words, it can be described as an autocrine-paracrine effect, involving secretion of growth factors by cells expressing polyomavirus Tag, that may be responsible for recruiting to proliferate Tag-negative cells in polyomavirus-associated human tumors. This explains the ability of polyomaviruses to interfere with the cell cycle during oncogenic transformation. Subsequently, the cell cycle is manipulated and the sequestration of p53 via LTag, results in accumulation of gene mutations in the infected cells causing the transformation without the actual support of viral components [19&20]. In conclusion, it may be interesting to decipher the role of other genes and non-coding RNAs such as miRNA or LnCRNAs (described in the previous sections) differentially expressed in PCa, in conjunction to their association with p53 upon LTag binding. The model described below depicts one such connection between BKV-mediated upregulation of MALAT-1 expression among AA and EA populations with PCa as MALAT-1 might represent a biomarker for p53 deregulation and modulate those differences.

However, it cannot be underestimated that more work is required to unravel the molecular mechanism underlying the viral oncogenic activity and understand the basis of oncogenic virus interference within the tumor microenvironment, thereby driving tumor progression (Figure 4) [49].

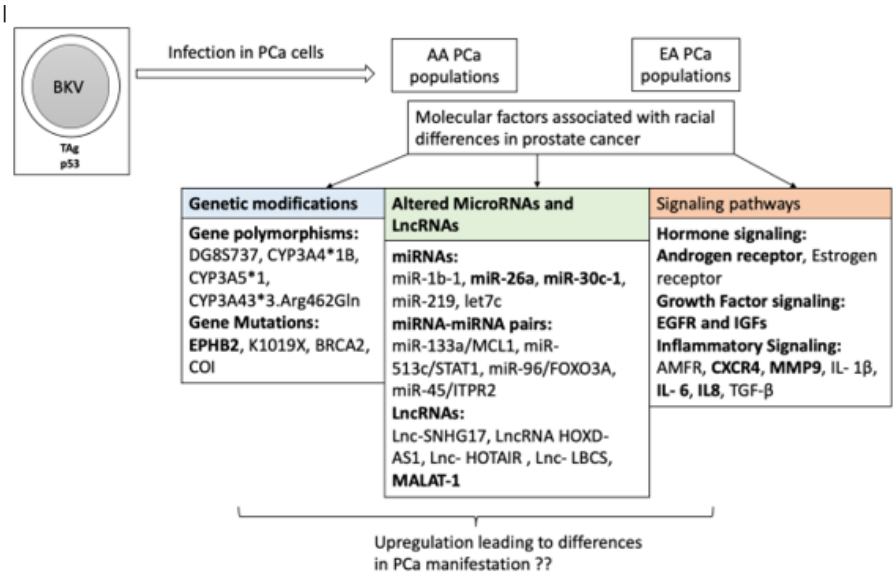

Figure 4: Model elucidating BKV mediated upregulation of different potential molecular factors underlying ethnic differences in prostate cancer. Some of the key target biomolecular (highlighted in bold) may represent a biomarker for p53 deregulation and associated prostate cancer progression (List of genes adapted from [49].

Conclusions- Racial disparities in PCa and way forward

The racial heterogeneity representing the African diaspora comprises of west African descendants who had migrated to the US, and thus classified as African- American. The geographic ancestry varies among African, European, and Native American groups.

Factoring in an individual's race/ethnicity are instrumental for understanding the underlying mechanistic racial profile differences in cancer and other diseases. Differences in prostate cancer risk could be attributed to tumor gene expression profiles that in turn could be largely associated to heritable factors as well as other non-biological factors.

Important developments pertaining to racial heterogenetic profiles can leverage the impact of difference in treatment regimens due to systemic racism on tumor biology. Thereby, resulting in profound impacts on health policy and disease prevention to improve and mitigate racial disparities in healthcare. Albeit, a significant proportion of research has been conducted to address these disparities, more evaluative future studies require the inclusion of diverse patient populations with a focus on marginalized communities.

Genomic and molecular investigations of PCa owing to racial heterogeneity have identified molecular signatures that may serve as therapeutic targets, paving a way for development of targeted cancer therapies. In addition, tumor virology as a field is still not greatly established and needs more attention to determine the role of viruses in etiology of cancer progression. The classical Koch's postulates, formulated to demonstrate the etiologic role of microorganisms in infectious diseases, cannot be applied to prove the viral etiology of human tumors directly. Among various reasons, the ubiquitous nature of viruses in human tumors, which produce a persistent or latent infection in human tissues or eventual dilution of viral episome due to lack of replication. Therefore, detection and prevalence of viruses in human tumors does not establish causation. More direct efforts should be considered in order to evaluate the oncogenic potential of viruses in human cancers. Lastly, designing studies to fully characterize viral oncogenic differences in tumor heterogeneity across racial/ethnic groups and identifying key biomarkers for treatment that are effective across all PCa patients can revolutionize the field of tumor virology.

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Conflict of interest

No conflict of interest.

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