

Forum

Molecular Discriminators of Racial Disparities in Prostate Cancer

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Recent molecular characterization of prostate cancer (PCa) identified novel genetic aberrations and disease subtypes. The frequencies of molecular aberrations show racial disparity. Clinical strategies and targeted therapies embracing these racial differences are required. Here we discuss ethnic differences in genetic alterations and their impact on the susceptibility, progression, and treatment of prostate cancer.

Introduction

PCa often harbors pathological and molecular intratumoral and interpatient **heterogeneity** (see [Glossary](#)) [1]. Racial differences in PCa prevalence have recently become the focus of many epidemiologic studies, but the underlying molecular mechanisms of ethnic disparity remain poorly understood. Studies by several groups demonstrated that African-American men with PCa tend to have higher serum estradiol and **prostate-specific antigen (PSA)** levels, advanced-stage cancer, and overall poorer survival than Caucasian-American men. By contrast, Asian men have lower disease prevalence compared with Asian-American or American PCa cohorts [2]. Despite lower PCa incidence, the Asian populations have a higher prevalence of advanced disease, probably due to the paucity of molecular and cancer screening methods, sensitive diagnostic tools, and strategies required for early detection. Heterogeneity in prostate cancer can be studied from biopsy

specimens containing multiple focal regions with differing **Gleason scores**. The samples can be subcategorized based on known molecular biomarkers such as *TMPRSS2-ERG* fusion, *SPINK1* overexpression, *PTEN* deletion, and *c-MYC* amplification status [3,4]. While much is known about interpatient molecular subtypes in Caucasian populations, detailed understanding of the molecular heterogeneity and disease progression in other ethnic groups is required.

PCa: Risk-Associated Susceptibility Genes

High-throughput studies identified genetic aberrations in PCa and their association with cancer susceptibility and familial risk. **Single nucleotide polymorphisms (SNPs)** in many risk-associated loci, including the 8q24 locus, have been positively associated with increased risk of cancer and higher PSA levels, Gleason score, and mortality. Furthermore, somatic amplifications at the 8q24 locus, a frequent genetic event, indicate that risk alleles in this locus may trigger the amplification of the entire region. Polymorphisms in the 8q24 locus confer increased susceptibility for PCa in Americans with African ancestry [5]. Fine mapping of the 3.8-Mb region at 8q24 demonstrated discrepancies across multiethnic populations with European, African-American, and Japanese ancestries [6]. It remains to be established whether the presence of risk alleles at 8q24 influences the regulation of neighboring genes such as *c-MYC* and *FAM84B*. Another possibility is the potential regulatory link between *PCAT1*, an oncogenic long non-coding RNA encoded by 8q24, and deregulation of *c-MYC* [7] and proximate genes.

Several independent studies showed that PCa patients harboring the *breast cancer 2, early onset (BRCA1/2)* germline mutation are at greater risk for early disease onset and have a higher likelihood of developing locally advanced and metastatic disease. Multi-institutional integrative **clinical sequencing** of biopsies of metastatic castration-resistant PCa

Glossary

Clinical sequencing: comprehensive examination of a patient's germline and somatic alterations within the genome using high-throughput sequencing techniques. Clinical sequencing has been instrumental in designing tailored medicine based on the individual's genotype, personal mutations or aberrations, and correlation with disease-susceptibility genes.

Genetic translocation: genetic rearrangement in which a segment breaks off from one chromosomal arm and fuses to the arm of another chromosome; may result in gene fusions.

Gleason score: a unique grading system used to evaluate PCa prognosis using biopsy specimens that is solely based on the architectural pattern of the tumor. Scoring is based on the differentiation pattern of the tumor biopsy, where a score of <6 means a well-differentiated tumor and >6 means a least-differentiated tumor.

Intergenic deletion: spontaneous deletion of a genomic region between genes resulting in genetic alterations.

Prostate-specific antigen (PSA): kallikrein-like serine protease synthesized by prostate epithelial cells. It is a major protein found in semen and is involved in liquefaction of the seminal coagulum. Healthy men have serum PSA levels <4 ng/ml; this concentration is usually used as a cut off for estimating PCa risk.

Single-nucleotide polymorphism (SNP): a single-nucleotide genetic variation at a specific position in the genome that may predispose an individual to a disease state.

Tumor heterogeneity: heterogeneity can exist within tumors of different individuals (intertumor heterogeneity) or be defined as subclonal diversity within the tumor of a single patient (intratumor heterogeneity).

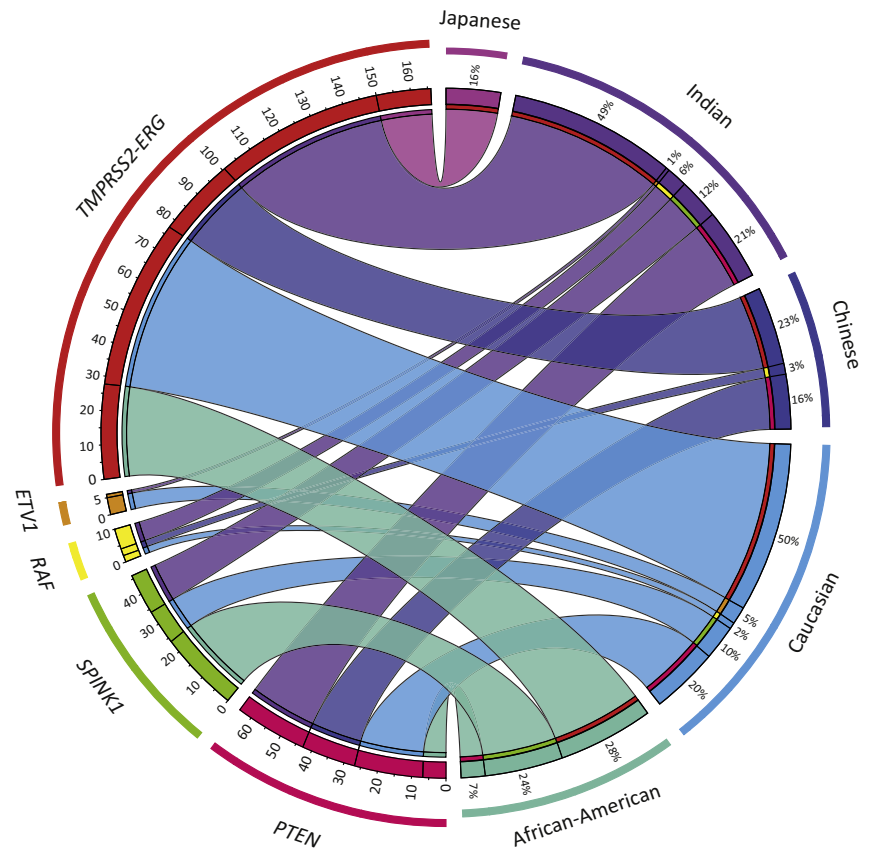
tumors revealed somatic and pathogenic germline alterations in *BRCA2* (~12.7% of cases), with 90% of cases harboring biallelic loss of *BRCA2* [8]. This finding suggests that treatment with poly(ADP-ribose) polymerase 1 (PARP1) inhibitors might be effective in patients with this molecular subtype. In light of the available treatment options, investigating *BRCA1/2* mutation frequency among patients in other ethnic groups is necessary. Intriguingly, a recent study shows mutation in *Homeobox B13 (HOXB13)* (G84E, rs138213197) at a higher frequency among men of European descent with either early onset of disease or a positive family history. This association was not

found in patients of African or Asian ancestry.

Incidence of *TMPRSS2-ERG* Fusion and *SPINK1* Overexpression across Diverse Ethnic Groups

The genetic rearrangements involving erythroblast transformation-specific (*ETS*) transcription factors (*ERG*, *ETV1*, *ETV4*, *ETV5*, and *FLI1*) represent the primary oncogenic aberration in a majority of prostate cancers [3]. About 50% of PCa patients harbor the *TMPRSS2-ERG* genetic rearrangement involving the androgen-driven *TMPRSS2* promoter, resulting in aberrant overexpression of the ERG oncoprotein [3]. Studies from several groups, including ours, have shown racial differences in the frequency of this genetic event. *ERG* aberrations are highly prevalent among Caucasian-American (~50%) and Indian (49%) patients. By comparison, African-American and Asian patients have significantly lower frequencies of around 30% and 10–20%, respectively (Figure 1) [4,9,10]. Conversely, African-American patients with ERG-negative status show higher-grade tumor indices and a less favorable clinical outcome [9]. A recent study that compared younger patients and older men with PCa suggested an association between age and higher incidences of *TMPRSS2-ERG* genetic rearrangement.

These proportions are nearly reversed for the subtype characterized by overexpression of *SPINK1*, which represents the second largest and more aggressive subset of PCa. Caucasian and Indian patients show ~10–15% frequency of *SPINK1* overexpression in a largely mutually exclusive manner with *ERG* aberration [4,11]. By contrast, African-American men showed nearly twice the frequency (~24%) [11]. Mutations in Speckle-type POZ (*SPOP*) in ERG-negative tumors define another molecular subtype [12]. Recently, *SPOP* mutations were found in ~10% of patients with localized tumors, and there was an overlap between



Trends in Cancer

Figure 1. Racial Differences in Prostate Cancer (PCa) Molecular Subtypes. Integrated Circos plot shows the correlation between molecular subtypes of PCa and their prevalence in different ethnic groups. Individual ethnic groups (on the right) are represented in different colors and corresponding colored ribbons connect each ethnic group to various molecular aberrations (on the left). The width of the individual ribbon denotes the prevalence of a molecular subtype in a given ethnic group.

SPINK1-positive status, mutations in *SPOP*, and deletion of *CHD1*, a chromatin remodeling factor. This distinct molecular subtype also shows mutual exclusivity with *ETS* rearrangements [1]. *SPOP* mutations were less frequently observed among African-Americans than in Caucasians [11]. It will be compelling to investigate the *SPOP* and *CHD1* mutation frequency in other ethnic groups. Taken together, these data suggest that molecular subclassification of PCa is highly warranted across different ethnicities and could help our understanding of disease heterogeneity and assist in the design of tailored therapies. Future studies will provide more detailed information on the pathobiology associated with these molecular subtypes.

Differential Genesis of *TMPRSS2-ERG* Fusion in Prostate Cancer

The genesis of *TMPRSS2-ERG* fusion through **intergenic deletion** is more prevalent in African-Americans than in Caucasian and Japanese patients [10]. *TMPRSS2-ERG* is associated with more aggressive tumors. Loss of *ETS2*, a potential tumor suppressor gene located between the *TMPRSS2* and *ERG* genes on chromosome 21, is likely to contribute to this aggressive phenotype (Figure 2A).

Chinnaiyan and colleagues demonstrated that androgen signaling induced spatial proximity of the *TMPRSS2* and *ERG* genomic loci (both located on 21q22) and that this is an important factor in gamma-irradiation-induced DNA double-strand breaks

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