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Seminars article

Enriching gene expression profiles will help personalize prostate cancer management for African-Americans: A perspective

Srinivasan Vijayakumar[a,b], John C. Henegan[c], Xu Zhang[d], Wanmei Wang[d], William A. Day[g], Vani Vijayakumar[e], Carlos S. Moreno[h,i], Christian R. Gomez[a,b,f,*]

[a] *Department of Radiation Oncology, University of Mississippi Medical Center, Jackson, MS*
[b] *Cancer Institute, University of Mississippi Medical Center, Jackson, MS*
[c] *Division of Hematology/Oncology, Department of Medicine, University of Mississippi Medical Center, Jackson, MS*
[d] *Department of Data Science, University of Mississippi Medical Center, Jackson, MS*
[e] *Department of Radiology, University of Mississippi Medical Center, Jackson, MS*
[f] *Department of Pathology, Department of Medicine, University of Mississippi Medical Center, Jackson, MS*
[g] *Department of Biology, Mississippi College, Clinton, MS*
[h] *Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA*
[i] *Winship Cancer Institute, Emory University, Atlanta, GA*

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Abstract

Prostate cancer (PCa) remains the most common form of cancer affecting men in the Western Hemisphere. Mortality rate is 130% higher among African-American men (AAM) than Caucasian-American men. As this trend is not new nor changing, there is an urgent need to identify markers with the ability to specifically distinguish aggressive PCa in the context of race. Gene expression patterns have been used as a tool to identify prognostic biomarkers for PCa to help reduce this disparity. Gene expression profiles reveal molecular mechanisms useful in understanding the biologic basis of tumorigenesis. Thus far, gene expression profiling analyses focused on race between AAM and Caucasian-American men (CAM) demonstrated distinct tumor microenvironments in the tumor-adjacent stroma and pathways associated with inflammation, lipid metabolism, and regulation of epithelial-to-mesenchymal transition. Additionally, we and others have established that hypoxia, another component of the tumor microenvironment, can been linked to malignant progression, metastasis, resistance to therapy, and poor clinical outcome in PCa. Gene expression panels, including distinct components related to the biology of PCa in AAM, may increase prognostic accuracy for this ethnic group. Furthermore, reference gene expression patterns, especially in the context of the emerging molecular taxonomy of PCa, would be buttressed by including more AAM in their development to consider the aspects of expression profiles differentially associated with race.

Keywords: mRNA; Gene expression profiling; Hypoxia; African-American men; Caucasian-American men

Introduction

Prostate cancer (PCa) remains the most common form of cancer affecting men in the Western Hemisphere. In 2017, 161,360 new cases of PCa are expected to occur in the United States and 26,730 deaths are expected nationwide [1]. The mortality rate is 130% higher among African-American men (AAM) than Caucasian-American men (CAM) [2,3]. This trend is not new or changing, as data from 1975 to 2007 indicate that the higher mortality rates of PCa among AAM have not narrowed when compared to CAM [4].

The disparity in PCa outcomes within the United States has been attributed to several factors [5–7], including differences in socioeconomic status and lifestyle exposures, access to health care, racial and ethnic discrimination, language and cultural barriers, and a delayed disease diagnosis in socioeconomically deprived communities [8]. These may contribute to or compound health delivery disparities as AAM, relative to CAM, are less likely to undergo primary definitive treatment when grouped by

* Corresponding author. Tel.: +1-601-815-3060; fax: +1-601-815-6806.
E-mail address: crgomez@umc.edu (C.R. Gomez).

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National Comprehensive Cancer Network-based risk groups, have more advanced disease when first diagnosed with cancer, show faster tumor volume growth, present with higher plasma prostate-specific antigen (PSA), and exhibit more adverse pathological findings in radical prostatectomy specimens [9], when compared to CAM [10,11]. Whether these differences translate into clinically meaningful readouts remains a matter of discussion. Rather than using the biologically imprecise divider of race, however, reliable biomarkers are needed to predict clinical outcomes to aid clinicians and patients in management decisions for all patients with PCa.

In this article, we hypothesize the following: (1) the typical PCa microenvironment is different between AAM and CAM; (2) differences in the typical PCa microenvironment contribute to a more aggressive phenotype of PCa in AAM; (3) differences in the PCa microenvironment may be detected through distinct molecular markers; and (4) studying in detail the molecular markers, and in particular gene expression profiles, of PCa specimens will lead to more accurate prognostic information which, in turn, will lead to changes in management that will produce better PCa-related outcomes, including those among AAM.

Materials and methods

In September 2016, one literature search of all studies published from August 2001 to July 2016 was conducted using PubMed and Scopus. The criteria used included as "gene expression profiles" AND "prostate cancer" AND "Caucasian-American Men" OR "African-American Men".

Other literature was identified using the reference lists of the selected articles. Only scientific articles written in English were considered for inclusion. Two reviewers (C.R.G. and W.A.D.) independently extracted data from selected studies using a standardized data extraction form. Any disagreement was discussed and reached a consensus for all issues. Studies that reported curated gene expression data related to clinical and pathological aspects were selected. Selected criteria collected from each study included list of authors, year of publication, geographical location, platform for mRNA expression analysis, sample size, and clinical and pathological variables (e.g., Gleason score [GS], tumor stage, lymph node and bone metastasis status, and prognosis).

To assess for hypoxia-associated genes with differential expression between AAM and CAM, an in silico analysis was performed. Publically available microarray gene expression dataset from Gene Expression Omnibus (GSE41967, http://www.ncbi.nlm.nih.gov/geo) deposited by Powell et al. [12] was used. Powell's team performed quantile normalization using the "qn" function in the R SRMA package, together with necessary quality control checks. The downloaded array data were transformed into Log 2 scale to correct skewed distribution. The transformed array data were used for all statistical analyses. We focused on this dataset because the metadata included information on both race and GS. We particularly focused on the associations between GS and ethnicity for 24 hypoxia-sensitive genes previously reported by us as significantly overexpressed in PCa relative to normal adjacent stroma [13].

Results

Gene expression profiles currently available in PCa diagnosis and management

During the last decade, there has been a continuous increase in new molecular biomarkers for different tumor types, leading to a refinement in their classifications [14,15]. The discovery of these biomarkers has been aided by technological innovations such as gene expression profiling arrays, differential display, serial analysis of gene expression, and next-generation sequencing [14,15]. Each of these techniques allowed for discovery and validation of biomarkers by correlating gene expression profiles and biological tumor characteristics. However, not all areas of oncology have been equally affected, and in PCa there is a need for novel PCa-specific prognostic biomarkers [16–18] beyond the PSA. The PSA test serves both to risk-stratify men at the time of diagnosis to assist in appropriate treatment decisions and to monitor for disease recurrence after definitive local therapy. However, its use in monitoring disease progression after recurrence is inadequate, and additional or improved biomarkers are needed in this space. This need is underscored by evidence that stopping therapy due to PSA progression alone would lead to some men not realizing the full benefit of therapeutic options [19].

Outside of the PSA test, different biomarker tests may be used during initial disease evaluation. These assays may predict if benign prostatic conditions or malignancy are present, and, in the setting of malignancy, prognosticate for indolent vs. aggressive PCa. Helping to predict whether benign prostatic conditions or PCa is more likely to be detected on further invasive testing can help men avoid repeat prostate biopsies. The Progensa PCa gene 3 (PCA3) test may be used for men suspected of having PCa despite a negative prostate biopsy [20]. The test is based on the in vitro amplification of PCA3, a prostate-specific long noncoding RNA whose transcript is overexpressed in the postdigital rectal examination urine of men with PCa compared to men without PCa [21]. The urine specimen for PCA3 analysis is easily obtained after digital rectal examination and may be incorporated into an algorithm designed to reduce the number of attempted prostate biopsies.

Biomarker tests based on gene expression signatures are also available for use in clinical practice to distinguish aggressive PCa from indolent disease, helping to assist in