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Platinum Priority – Prostate Cancer

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The Diverse Genomic Landscape of Clinically Low-risk Prostate Cancer

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Abstract

Background: Among men with clinically low-risk prostate cancer, we have previously documented heterogeneity in terms of clinical characteristics and genomic risk scores.
Objective: To further study the underlying tumor biology of this patient population, by interrogating broader patterns of gene expression among men with clinically low-risk tumors.
Design, setting, and participants: Prostate biopsies from 427 patients considered potentially suitable for active surveillance underwent central pathology review and genome-wide expression profiling. These cases were compared with 1290 higher-risk biopsy cases with diverse clinical features from a prospective genomic registry.
Outcome measurements and statistical analysis: Average genomic risk (AGR) was determined from 18 published prognostic signatures, and MSigDB hallmark gene sets were analyzed using bootstrapped clustering methods. These sets were examined in relation to clinical variables and pathological and biochemical outcomes using multivariable regression analysis.
Results and limitations: A total of 408 (96%) biopsies passed RNA quality control. Based on AGR quartiles defined by the high-risk multicenter cases, the University of California, San Francisco (UCSF) low-risk patients were distributed across the quartiles as 219 (54%), 107 (26%), 61 (15%), and 21 (5%). Unsupervised clustering analysis of the hallmark gene set scores revealed three clusters, which were enriched for the previously described PAM50 luminal A, luminal B, and basal subtypes. AGR, but not the clusters, was associated with both pathological (odds ratio 1.34, 95% confidence interval [CI] 1.14–1.58) and biochemical outcomes (hazard ratio 1.53, 95% CI 1.19–1.93). These results may underestimate within-prostate genomic heterogeneity.
Conclusions: Prostate cancers that are homogeneously low risk by traditional characteristics demonstrate substantial diversity at the level of genomic expression. Molecular substratification of low-risk prostate cancer will yield a better understanding of its divergent biology and, in the future may help personalize treatment recommendations.
Patient summary: We studied the genomic characteristics of tumors from men diagnosed with low-risk prostate cancer. We found three main subtypes of prostate cancer with divergent tumor biology, similar to what has previously been found in women with breast cancer. In addition, we found that genomic risk scores were associated with worse pathology findings and prostate-specific antigen recurrence after surgery. These results suggest even greater genomic diversity among low-risk patients than has previously been documented with more limited signatures.

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1. Introduction

Among human malignancies, prostate cancer is remarkable both for its pervasiveness and for its exceptionally variable natural history. Roughly one man in six is diagnosed in his lifetime, a high outlier incidence that belies an even higher histological prevalence as indicated by autopsy studies [1]. A large majority of prostate cancers are entirely quiescent, and would never cause any symptoms or loss of life years if undiagnosed; yet the fraction that are more aggressive still amount to the second leading cause of cancer death among men [2]. Recent molecular studies among higher-risk tumors have documented genomic heterogeneity to match prostate cancer's clinical variability [3,4].

Clinical risk stratification of prostate cancer at diagnosis is relatively accurate in identifying cancers unlikely to progress to clinically relevant stages [5], and can be further enhanced through imaging and/or use of prognostic biomarker signatures [6]. Such approaches, however, assess aggressiveness along only one or a few biological axes, and do not allow the sort of molecular subtyping that is now standard for other tumors such as breast cancer. In fact, recent studies of high-risk prostate cancers have identified luminal and basal subtypes that echo those found in breast cancer and other cancers to a remarkable degree [7].

Active surveillance (AS) rather than immediate treatment is now widely endorsed as a preferred management strategy for low-risk prostate cancer [8,9] and is offered to a growing proportion of men both in the USA [10,11] and internationally [12]. An important goal of contemporary investigation into the biology of low-risk prostate cancer is to help determine which of the low-grade prostate cancers are highly aggressive and merit immediate treatment, need close AS, and could be safely followed with a less active monitoring strategy. We aimed to characterize the genomic expression patterns of tumors with relatively homogeneous, low-risk clinical characteristics, to determine whether such tumors are characterized by similarly homogeneous expression patterns, both in terms of genomically determined clinical risk and in terms of tumor subtyping based on broader expression analysis.

2. Patients and methods

Paraffin-embedded prostate biopsy specimens were collected from 427 men who underwent radical prostatectomy at the University of California, San Francisco (UCSF), based on patient treatment preference, for tumors that would have been eligible for AS based on low-risk (clinical stage ≤T2N0M0, prostate-specific antigen [PSA] ≤20 ng/ml, and biopsy grade group 1) or low-volume (≤3 cores positive overall) grade group 2 tumor characteristics. Additional inclusion criteria were at least 1 mm of cancer on biopsy, prostatectomy slides available for review, and provision of informed consent under institutional review board supervision. Clinical risk was summarized using the extensively validated Cancer of the Prostate Risk Assessment (CAPRA) score [13].

Biopsies and prostatectomy slides were centrally reviewed for grade and stage (by J.P.S.), and RNA was extracted as previously described [14]. In cases with multiple positive biopsy cores, the core with the longest length of the highest-grade cancer was selected. RNA from each case was amplified and labeled using the Ovation FFPE WTA system (NuGen, San Carlos, CA, USA) and hybridized to a Human Exon 1.0 ST GeneChip (Affymetrix, Santa Clara, CA, USA).

The UCSF cases in this study, as with similar prior studies of biopsy-based genomic risk assessment, were restricted by design to low/low-intermediate risk cases. For comparison, and to provide a wider dynamic range of genomic risk, we analyzed prostate cancer cases in the Decipher Genomic Resource Information Database (GRID), a prospective, genome-wide expression registry for urological oncology (NCT02609269), which includes basic demographic and baseline clinical information. These cases were profiled as part of clinical care to facilitate a variety of treatment decisions per clinician discretion. All 1290, mostly higher-risk prostate biopsy, cases currently represented in the GRID were included. For GRID cases, the needle biopsy core with the highest grade and percentage of tumor was selected for RNA extraction and purified using the RNeasy FFPE kit (Qiagen, Valencia, CA, USA), and amplified, labeled, and hybridized as described above for the UCSF cases.

Both GRID and UCSF samples were processed in a Clinical Laboratory Improvement Amendments (CLIA/CAP)-certified laboratory (GenomeDx Biosciences, San Diego, CA, USA). Quality control, normalization and gene level summarization, and batch effect correction were performed using Affymetrix Power Tools (v 1.19.0), Single Channel Array Normalization [15], and ComBat [16], respectively.

2.1. Pathway summarization and average genomic risk

The Molecular Signatures Database (MSigDB) was queried for 50 hallmark gene sets [17]. Non–prostate or non–cancer-related gene sets were filtered, leaving 37 gene sets for the analysis. Each hallmark set includes a variable number of genes (ranging from 32 to 200) and summarizes expression related to the given biological process. Hallmark gene sets are further grouped into seven biological process categories based on highly correlated expression profiles [17]. Hallmark gene set scores were computed by averaging the expression of each gene in the set, excluding genes not captured by the array.

A substantial number of genomic expression risk scores have previously been published, and we adapted them to the array, as previously described [18]. Eighteen prognostic signatures that achieved univariate significance for the metastasis endpoint in the study were combined into an average genomic risk (AGR) score [18] for each patient by computing the mean of their normalized scores. This AGR score, which serves as a genomic metascore, was analyzed with respect to clinical outcomes.

2.2. Clustering analysis

Patient pathway expression profiles were partitioning around medoids (PAM) clustered based on Spearman's correlation distances. Consensus clustering [19] bootstrapped over 1000 iterations with 80% sampling of both patients and pathways was used to arrive at a robust clustering solution. Pathway cluster expression patterns were specifically examined in reference to the PAM50 genomic classifier originally developed for breast cancer, and recently found to identify patterns in prostate cancer highly analogous to tumor subtypes described as “luminal A,” “luminal B,” and “basal,” which are prognostic in prostate cancer and strongly predict response to androgen deprivation therapy in particular [7]. Subset analyses focused on men with Gleason grade group 1 tumors on biopsy and on those confirmed at prostatectomy to have a “pure” Gleason grade group 1 tumor on final pathology.

2.3. Statistical analysis

Univariate association between genomic consensus clusters and clinical variables were tested using Kruskal-Wallis and Fisher exact tests with

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