Panomic assessment reveals DNA repair alterations are common in prostate cancer (PC) and predicts potential therapeutic response to taxane-platinum combination therapy

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Abstract (# 5040)

***Final analysis included an additional 81 patients*

Background: Patients with PC have limited treatment options after failure of hormonal and taxane therapy. Androgen receptor (AR) signaling may exert therapeutic effects on the DNA repair pathway in PC. We have assessed the proteomic/genomic DNA repair aberrations in primary (P) and metastatic (M) PC and explored the therapeutic implications of these mutations using panomic next generation sequencing (NGS). We hypothesized that there is a differential in gene expression and mutation between P and M tumors.

Methods: Molecular profiles of 437 PC tumor samples were defined. Protein expression (IHC), gene amplification (ISH) and sequencing (NGS) were performed. A panel of 30 DNA repair genes was used to define DNA repair intact (DRI) and DNA repair deficient (DRD) subgroups. Unclassified variants were included for analysis. Pearson's chi-squared test was used to test for significant differences.

Results: Biopsies from 437 PCs (median age 67) were studied. Specimens submitted for profiling included 158 P PCs (36%) and 279 M PCs (64% [18% bone; 37% visceral; 24% lymph nodes; 21% other sites]). The most frequently mutated DNA repair genes included TP53 (31%), ERCC5 (19%), FANCG (16%), MSH6 (13%), POLE (10%), PMS1 (13%), PTEN (9%) and BRCA2 (6%). Functional protein loss as measured by IHC was seen in ERCC1 (44%), MGMT (39%), and PTEN (43%). In a limited cohort of patients tested using a 592-gene hybrid-capture NGS, 26/31 (84%) had alterations in at least 1 DNA repair gene. DRD PC exhibited higher expression rates of AR (57% vs. 20%; p=.048) and TOPO1 (88% vs. 40%; p=.02) than DRI PC. An optimal taxane therapeutic response profile was observed in 20% of DRD tumors. Significant differences between P and M tumors were seen in ERCC1, AR, ATM and TP53. M tumors had significantly increased expression of TOP2A, TS and TUBB3.

Conclusion: DNA repair defects are common in PC with a difference in gene expression and mutation between P and M tumors. Differential expression between African American and Caucasian patients and further classification of variants are currently being assessed. Taxane-platinum combination chemotherapy should be tested specifically in DRD PC.

Background

- There are few therapy options for advanced refractory prostate cancer
- Recent data have shown metastatic prostate cancer patients:
  - ✓ with DNA repair deficiencies (BRCA, ATM) respond to PARP inhibitors (olaparib)[1]
  - ✓ have longer overall survival when treated with chemo[docetaxel]-hormonal therapy vs. androgen-deprivation therapy (ADT) alone[2]
- AR signaling evolves during the progression of prostate cancer and has been shown to directly regulate genetic activities and pathways that influence DNA damage repair mechanisms[3,4]
- We sought to explore complex relationships between DNA repair genes, biomarkers predictive of chemotherapy and androgen receptor status in primary vs. metastatic prostate cancers to identify novel therapy approaches, and potentially new combination strategies

Methods

518 advanced prostate cancer patients were included in this analysis and tested centrally at a CLIA laboratory (Caris Life Sciences, Phoenix, AZ). Tests included one or more of the following: gene sequencing (MiSeq and NextSeq Illumina platforms), copy number variation (NextSeq Illumina) and protein expression (immunohistochemistry [IHC]). Cutoff for PTEN, ERCC1 and MGMT : >10% is positive. AR High is defined as 3+ 100% staining. Additional cutoffs and antibodies are available upon request.

Results

Tumor and Patient Parameters

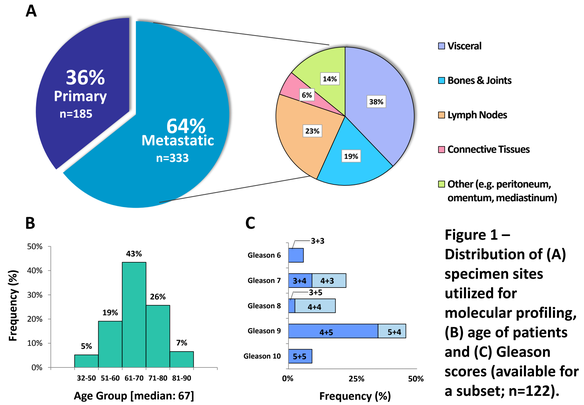


Figure 1 – Distribution of (A) specimen sites utilized for molecular profiling, (B) age of patients and (C) Gleason scores (available for a subset; n=122).

Results

Table 1. DNA Damage Repair Genes assessed in this study
[highlighted genes are regulated by or direct target genes of AR signaling; *DNA repair status panel]

Gene	Platform	DNA Damage Repair (DDR)	Gene	Platform	DNA Damage Repair (DDR)
PTEN	NGS; IHC	damage signaling (indirct); DSB; NER	MRE11A*	NGS	damage signaling; DSB repair; oxidative stress
TP53	NGS	damage signaling; DSB	MUTYH*	NGS	MMR
ERCC1*/2*/3*/4*/5	NGS; IHC (ERCC1)	NER	POLE*	NGS	damage signaling
BRCA1*/2*	NGS	HR; damage signaling	RAD51*/51B*/50	NGS	HR; damage signaling; DSB repair
MLH1*/MSH2*/MSH6*PMS1*/PMS2*	NGS	MMR	WRN*	NGS	HR, BER
ATM*/ATR	NGS	HR; damage signaling; DSB; oxidative stress	XPA	NGS	NER
ATRX	NGS	NHEJ; DSB	PALB2	NGS	HR; damage signaling
DDB2	NGS	damage signaling	ATRX	NGS	NHEJ
BLM*	NGS	HR	NBN*	NGS	DSB
CHK1*/2*	NGS	HR; damage signaling	BARD1	NGS	HR
FANCA*/C*/D2*/E*/F*G*/L*	NGS	HR; ICL repair	BRIP1	NGS	HR; damage signaling
PRKDC*	NGS	NHEJ			

MMR (mismatch repair); DSB (double strand break); NHEJ (non-homologous end-joining);
HR (homologous repair); BER (base excision repair); NER (nucleotide excision repair)

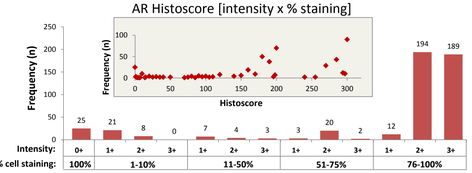


Figure 2- Distribution of AR staining in prostate cancer patients (n=488) and conversion of immunohistochemistry results into histoscore (inset).

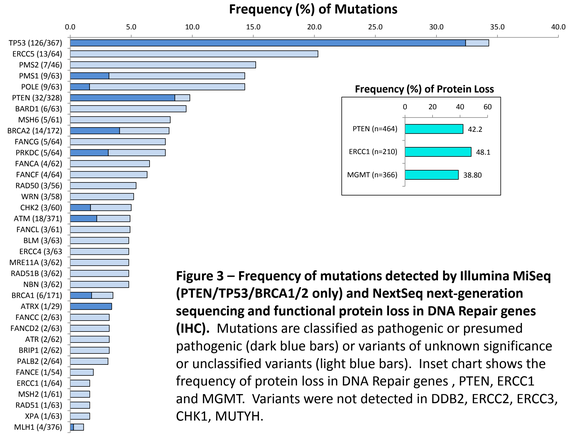


Figure 3 – Frequency of mutations detected by Illumina MiSeq (PTEN/TP53/BRCA1/2 only) and NextSeq next-generation sequencing and functional protein loss in DNA Repair genes (IHC). Mutations are classified as pathogenic or presumed pathogenic (dark blue bars) or variants of unknown significance or unclassified variants (light blue bars). Inset chart shows the frequency of protein loss in DNA Repair genes , PTEN, ERCC1 and MGMT. Variants were not detected in DDB2, ERCC2, ERCC3, CHK1, MUTYH.

Results, contd.

Comparison of DNA Repair Deficient (DRD) and Intact (DRI) Prostate Cancers

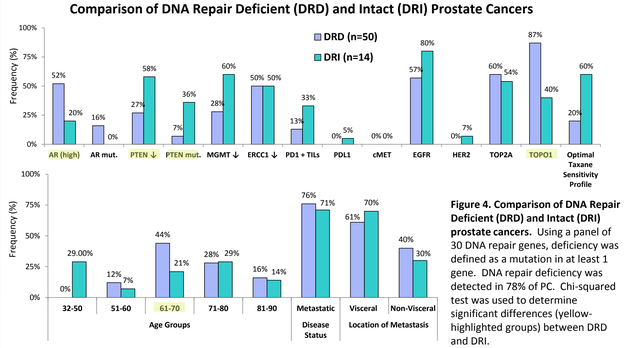
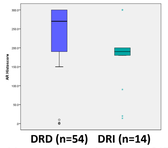


Figure 4. Comparison of DNA Repair Deficient (DRD) and Intact (DRI) prostate cancers. Using a panel of 30 DNA repair genes, deficiency was defined as a mutation in at least 1 gene. DNA repair deficiency was detected in 78% of PC. Chi-squared test was used to determine significant differences (yellow-highlighted groups) between DRD and DRI.



Measure of Association: p=0.047

Figure 6 – Box Plot comparing AR Histoscore to DNA Repair Status

Biomarker Differences in Primary and Metastatic Prostate Cancers

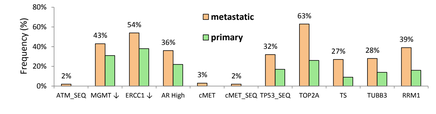


Figure 7. Biomarker differences between primary and metastatic PC. Biomarkers include those tested by IHC (MGMT, ERCC1, cMET, TOP2A, TS, TUBB3 and RRM1) and sequencing (ATM, cMET, TP53). Only biomarkers showing statistical differences (p<0.05) are shown.

Conclusions

- Panomic assessment reveals frequent alterations in DNA repair genes in prostate cancer
- DRD tumors associate with higher rates of androgen receptor staining, which supports previous *in vitro* findings[3,4] regarding the important role of AR/androgen signaling in DNA repair mechanisms. DRD tumors peak in the 61-70 age group and associate with higher rates of TOPO1. A taxane sensitivity profile is present in 20% of DRD tumors, suggesting a potential role for platinum-taxane combination in a subset of patients with DNA repair defects.
- PTEN loss and mutations associated with DRI tumors. Loss of PTEN has been implicated in genomic instability, whereby loss of function leads to lowered DNA repair rates (through interactions with DNA repair genes like p53 and Chk1) suggesting an alternate mechanism of reducing DNA Repair efficiency.
- Primary and metastatic PC exhibit differential protein expression and mutation rates, indicating therapeutic targets may change through the progression of disease, and the need for molecular profiling through the course of disease progression.

References

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