

Genomic analysis of a longitudinal series of surgical prostate cancer bone metastases and xenografts from the same patient revealed selection of a progressively therapy-resistant metastatic clone.

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Background: Prostate cancer metastasizes to bone in 50-90% of patients with advanced disease yet relatively little is known about genome-wide alterations in the prostate cancer bone metastases themselves. Recent genomic studies on prostate cancer have identified recurrent mutations and gene rearrangements such as the TMPRSS2-ERG fusion and variants of the androgen receptor (AR). In order to understand the changes that occur which may lead to progressive therapy resistance of the prostate cancer bone metastases we investigated the genomic and transcriptomic variation in a longitudinal series of surgical bone metastasis samples and xenografts derived from the same patient.

Methods: Surgical prostate cancer bone metastasis samples were collected at the time of orthopaedic repair surgery and used to establish a new xenograft model, **PCSD1 (Prostate Cancer San Diego 1)**. We performed whole exome sequencing (WES), copy number variation (CNV) on whole genome SNP arrays, and transcriptome analyses on a unique set of longitudinal samples from one patient including: blood (germ line), primary prostate tumor, surgical bone metastasis sample #1 (after ADT and radiation, right femur), bone metastasis #2 (after ADT, radiation and docetaxel, left femur), bone metastasis #3 (after abiraterone, radiation, plus cabazitaxel, left femur). We also performed these analyses on intra-femoral PCSD1 xenograft tumors generated from the same patient to determine their exomic integrity compared to the patient samples and the impact of treatment. Genomic DNA sequencing was performed on the Illumina HiSeq 2000 sequencing platform. Affymetrix Oncoscan analysis was used to determine genome-wide CNV and loss-of-heterozygosity (LOH) profiles. Whole transcriptome analysis was performed using Affymetrix GeneChip Human Transcriptome Array 2.0.

Results: Comparison of whole genome CNV analyses of patient bone metastasis sample #1 and low passage PCSD1 intra-femoral xenograft showed they were almost identical. CNV analysis of the patient bone metastasis samples #1 and #2 showed they were significantly different. Surprisingly, patient bone metastasis sample #2 and high passage PCSD1 xenograft (derived from patient bone met sample #1) were very similar. Bicalutamide treatment of castrate-resistant intra-femoral PCSD1 xenografts induced large scale copy number loss and induced expression of a neuronal signature. Exome sequence analysis identified point mutations, SNVs, small insertion and deletions, translocations and additional gene rearrangements that were shared as well as unique to each bone metastatic sample.

Conclusions: Genome-wide copy number variation (CNV), and whole exome sequencing (WES) revealed selection of a *similar therapy-resistant sub-population* occurred in both the patient and in xenografts derived from the same patient. Analysis of surgical prostate cancer bone metastases at different stages of treatment and progression in this patient provides a foundation to profile genomic diversity in recurrent bone metastatic prostate cancer.

Conflict of Interest: No conflicts.

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