

Integrative genomics of prostate cancer progression: a pilot study

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Background: Primary prostate cancer (PPCa) often presents as multi-clonal, heterogeneous disease. To date, there is no systematic genomic study comparing distinct areas of PPCa to metastases. We report next generation sequencing (NGS) results on 10 PPCa and matched metastatic castration-resistant prostate cancer (mCRPC).

Methods: Whole exome sequencing (WES) data from frozen mCRPC were available through the SU2C trial and/or Precision Cancer Care. All pathology slides from corresponding radical prostatectomies were reviewed and distinct tumor areas were selected based on histology, Gleason score, topography and immunohistochemistry (ERG, p53), and processed separately for WES, PCR-based DNA-sequencing (DNAseq) and PCR-based RNA-sequencing (RNAseq). We performed WES-based phylogenetic reconstruction for each case and the clonality score for each PPCa area *versus* corresponding metastasis was calculated.

Results: WES was performed on 37 PPCa areas (2-6/case) and 13 mCRPC samples (1-2/case). DNAseq and RNAseq were performed on 53 PPCa areas (2-7/case). Neuroendocrine differentiation (NED) was noted in two PPCa and three mCRPC. Two patients carried *BRCA2* germline mutation, both with mCRPC with NED.

Gene alterations shared by PPCa and matched mCRPC included: *TP53*, *SPOP*, *PIK3CA*, *BRAF*, *FGFR3* and *MYC* point mutations or indels; and *PTEN*, *RB1* and *FANCA* deletions. The most frequent alteration found in mCRPC, but not in matched PPCa was *AR* amplification (5 cases) or activating point mutation (1 case); other altered genes included *ARID1A* (1 case) and *KDM4A* (1 case), suggesting a role of epigenetic regulators in mCRPC progression.

Clonality score and phylogenetic reconstruction were informative in six cases. Transcriptome analysis further supported relationship between genomically similar PPCa areas. Tumor purity variation across PPCa samples was the main limitation of these analyses.

Conclusion: Comparative NGS analysis can provide useful information to identify primary clone(s) that give rise to mCRPC. The study on an extended cohort (SU2C patients) is underway, with the potential to identify novel molecular drivers of metastatic progression and redefine histopathology criteria used to assess PPCa prognosis.

Conflict of interest: None.

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