Abstract citation ID: bvac150.1864

Tumor Biology

RF27 | LBSUN342

Ar-targeted Linked-read Sequencing Reveals Complex Ar Structural Variants In Castration Resistant Prostate Cancer Models

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Androgen deprivation therapies are employed for the treatment of advanced prostate cancer to suppress the transcriptional activity of the androgen receptor (AR). However, over the course of therapy, AR transcriptional activity re-emerges, and the disease progresses to castration resistant prostate cancer (CRPC). During CRPC progression, AR becomes heavily altered by genomic aberrations that include amplification, missense mutations, and structural variants (SVs). AR SVs are heterogeneous across CRPC specimens, with variability noted in SV class, breakpoint locations, and co-occurrence with amplification. Further variability has been observed for sub-clonal enrichment of AR SVs within tumors. A barrier to understanding the clinical significance of AR SVs is the challenge of deciphering this high degree of variability from short-read DNA-sequencing data. To address this challenge, we performed AR-targeted linked-read DNA-sequencing of CRPC cell line and patient-derived xenograft (PDX) models with the goal of resolving sub-clonal and complex AR SVs. We benchmarked this approach using prostate cancer cell lines and LuCaP86.2 PDX tissue harboring known AR SVs. Using this benchmarking approach, we identified linked AR SVs that co-occurred on single DNA molecules in LuCaP35CR and LuCaP105CR PDX models. We also identified a novel AR SV in the LuCaP77 PDX model and a castration-resistant derivative, LuCaP77CR. These results have revealed heterogeneous trajectories of AR SVs in CRPC and define a new class of complex AR SVs where multiple rearrangements co-occur on single DNA molecules to yield highly rearranged AR gene structures.

Presentation: Monday, June 13, 2022 1:05 p.m. - 1:10 p.m.