Comparative analysis of *AR* gene aberrations in circulating tumor cells and plasma cell-free DNA from prostate cancer patients

Background

Reactivation of the androgen receptor (AR) transcription factor is a key step in the progression to endocrine therapy resistance in castration-resistant prostate cancer (CRPC). One mechanism supporting the reactivation of AR signaling is the generation of constitutively active AR variants through genomic rearrangements that change the architecture of the *AR* gene. The landscape of *AR* gene rearrangements has been examined in solid tumor samples and plasma cell-free DNA (cfDNA) from CRPC patients. However, the detection of *AR* gene rearrangements in patient circulating tumor cells (CTCs) represents a gap in knowledge.

Methods

We used the Versatile Exclusion-based Rare Sample Analysis (VERSA) platform to capture CTCs and isolate DNA. DNA was subjected to whole genome amplification and analyzed using a targeted DNA-sequencing (DNA-seq) approach. DNA-seq data were analyzed by four different DNA structural variant (SV) detection algorithms and two different single nucleotide variant (SNV) detection algorithms. This CTC capture and analysis pipeline was first optimized using prostate cancer cell lines with known *AR* gene aberrations. Following optimization, we analyzed CTCs from ten patients with metastatic CRPC and compared the results with a parallel analysis of matched plasma cfDNA samples.

Results

Out of ten CRPC CTC samples analyzed, there was one sample harboring a 2.6 Mb inversion with one breakpoint occurring in intron 1 of *AR*, and the other breakpoint occurring within *ZC4H2*. This *AR* gene rearrangement was not detected in matched cfDNA. Conversely, two cfDNA samples were found to harbor *AR* gene rearrangements that were not detected in matched CTC samples. These findings demonstrated an unexpected discordance of *AR* gene rearrangement detection between liquid biopsy sources. Interestingly, we also observed discordance in the detection of *AR* T878A SNVs between matched CTC/cfDNA samples.

Conclusions

We optimized a CTC capture and analysis pipeline for detection of *AR* gene rearrangements in CRPC patient liquid biopsies. Comparing this pipeline to standard cfDNA analysis revealed that *AR* gene rearrangements and SNVs found in both liquid biopsy sources provide complementary information on *AR* gene aberrations. These findings suggest that analysis of CTC DNA and cfDNA may be necessary to obtain an accurate understanding of the *AR* gene aberration landscape in CRPC.