New Druggable Targets in ETS rearrangement-negative CRPC

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The TMPRSS2-ERG fusion is a well-known fusion in prostate cancer. However, this fusion lacks enzymatic activity, making it difficult to target with drugs. In light of this, our study sought to identify targetable gene fusions that could be used as therapeutic targets. Through transcriptome sequencing and whole genome sequencing analyses of 36 CRPC (Castration-Resistant Prostate Cancer) patients, we identified that 11% (4 out of 34) of ETS rearrangement-negative CRPC patients harbored BRAF fusions. We suggested that this fusion likely arose due to FOXO1 deletion, as indicated by whole-genome sequencing. Using AlphaFold, we predicted the structure of this fusion, revealing its structural similarity to BRAF V600E. When vemurafenib was administered to cell lines engineered to carry this fusion, there was a significant reduction in cell viability. This showed the potential for promising outcomes in treating CRPC patients with this fusion. This discovery goes beyond previous studies that have primarily focused on fusions activating downstream pathway signaling. Instead, our study demonstrates that structural differences can lead to opportunities for drug repositioning. Moreover, this finding has the potential to offer new biomarkers for CRPC patients, enhancing our understanding of the disease and opening doors to novel therapeutic approaches.