Phosphoproteome-guided multi-omic integration prioritizes kinases to co-target with the androgen receptor for drug synergy in prostate cancer

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Background: Metastatic castration resistant prostate cancer (CRPC) remains incurable due to the lack of effective therapies. Pathway activation of signaling proteins, such as kinases, are hypothesized to drive the progression of lethal CRPC after hormonal therapies. Due to the paucity of activating mutations of kinase genes in prostate cancer, alternative approaches are needed to uncover these aberrant signaling pathways so that they may be investigated rationally, and in combination, with hormonal therapies in relevant model systems.

Methods: We developed and published a new phosphoproteomic encyclopedia of prostate cancer cell lines and clinical tissues from lethal metastatic CRPC patients obtained at rapid autopsy using phosphopeptide enrichment coupled to quantitative mass spectrometry. A systematic computational approach was developed to integrate our phosphoproteomic dataset with gene expression, mutation, and copy number data that have previously been generated from these tissues as well as relevant prostate cancer cell lines to synthesize a robust signaling network consisting of a hierarchy of druggable kinase pathways for therapy.

Results: As an extension of our previous published analyses in the CRPC cohort, we generated a hierarchal ranking of kinases predicted to be active in three prostate cancer cell lines (LNCaP, 22RV1, and DU145) based on the combined knowledge of transcriptomic and phosphoproteomic data. The kinases SRC and DNAPK emerged as strong candidates and were predicted to be responsible for a majority of the kinase signaling observed in these cell lines. To functionally assess our predictions, we performed drug synergy studies with inhibitors targeting SRC, DNAPK, or chemotherapy (docetaxel) and used them in combination with enzalutamide. SRC and DNAPK combinations yielded strong synergy in concordance with our predicted kinase hierarchies for the respective prostate cancer cell lines while docetaxel did not result in such synergy.

Conclusions: Integration of phosphoproteomic and gene expression data yielded a hierarchy of kinases predicted to be active in prostate cancer cell lines. Our work nominated SRC and DNAPK activation as top candidates. Our results suggest that specific targeted combinations of SRC or DNAPK kinase inhibitors with enzalutamide may inform more potent, personalized therapeutic options in CRPC. Future work will uncover the mechanism of such synergy and develop methods to identify appropriate phosphoprotein biomarkers that will predict response to these combination therapies.

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