Phosphoproteome-Guided Integration Reveals Patient-Specific Signaling Networks in Lethal Prostate Cancer

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Background: Metastatic castration resistant prostate cancer (mCRPC) 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. We set out to define the global picture of signaling pathways in lethal prostate cancer through phosphoproteome-guided dataset integration.

Methods: We developed an extensive dataset of the phosphoproteome in mCRPC tissues and then integrated this data with other traditional datasets containing mRNA, mutations, and amplifications. This integration allowed for the development of comprehensive signaling networks that are both enriched and activated in this disease. We also developed patient-specific networks via this integration approach and included a rank-ordered list of kinases for targeted therapy both in patients and cell lines.

Results: We found that integration of the mCRPC phosphoproteome enriched for cancer hallmarks related to the PI3K/AKT, AR, DNA damage, and cell cycle pathways. For six individual patients, we revealed selective activity of these cancer hallmarks and termed these individual pathway profiles 'phosphorylation-based cancer hallmarks using an integrative personalized signature' (pCHIPs). Using these hallmarks, we created a hierarchy of kinase activation for each of these individual patients to aid in the prioritization of targeted therapies. The relevance of the kinase hierarchy was confirmed through evaluation of published datasets where prostate cancer cell lines were subjected to either pharmacological or genetic perturbation of the ranked kinases.

Conclusions: The integration of tissue samples from a single autopsy program allowed us to make inferences on the connections between different omic datasets. Our work sheds light into the diversity of the activated signaling pathways in individual mCRPC patients, while prototyping an integrative, pathway-based approach to drug prioritization in these patients.

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