Phosphoproteome Integration Reveals Patient-Specific Networks in Prostate Cancer

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ABSTRACT

Background: We set out to define the global picture of signaling pathways in lethal prostate cancer through dataset integration. **Methods:** We developed a complete and extensive new dataset of the phosphoproteome in metastatic CRPC by extending our analysis to phosphoserine and phosphothreonine peptides and then combining this information with our previously published phosphotyrosine peptide data (Drake et al., 2013). We used clinical tissue from lethal metastatic castration resistant prostate cancer (CRPC) patients obtained at rapid autopsy to evaluate diverse genomic, transcriptomic, and phosphoproteomic datasets for pathway analysis. Using Tied Diffusion through Interacting Events (TieDIE), we integrated differentially expressed master transcriptional regulators, functionally mutated genes, and differentially activated kinases in CRPC tissues to synthesize a robust signaling network consisting of druggable kinase pathways. We introduce a new tool called phosphorylation-based cancer hallmarks using integrated personalized signatures (pCHIPS) to establish patient-specific pathways marking key signaling events for possible targeting. **Results:** Using MSigDB hallmark gene sets, six major signaling pathways with phosphorylation of several key residues were significantly enriched in CRPC tumors after incorporation of phosphoproteomic data. Individual autopsy profiles developed using these hallmarks revealed clinically relevant pathway information potentially suitable for patient stratification and targeted therapies in late stage prostate cancer. Here we describe phosphorylation-based cancer hallmarks using integrated personalized signatures (pCHIPS) that sheds light on the

diversity of activated signaling pathways in metastatic CRPC while providing an integrative, pathway-based reference for drug prioritization in individual patients. **Conclusions**: We found cases in which different hallmarks were implicated with the patient-specific networks compared to using only the mutational information. Seven hallmarks were concordant across the patients, seven were discordant, and five agreed in a subset of patients. In addition, we used models derived from cell lines to investigate whether the presence of mutations or inferred activated kinases were more informative about drug sensitivity. The inferred phospho-based activities were as indicative of drug response as the presence of somatic mutations in those pathways and, when averaged across pathways and cell lines, these data suggest one type of data is sufficient to implicate pathway targets. Thus, for an individual patient afflicted with a tumor that lacks mutations in known actionable pathways, phosphoproteomic data could be informative to prioritize treatment.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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