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What can we learn from phosphoproteomics compared to transcriptomics in DNA damage and other processes?

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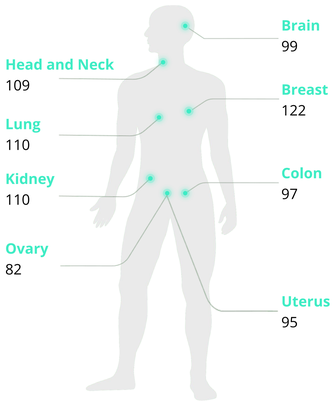
Background

With the recent availability of large scale multi-omics datasets, we studied the correlation between phosphorylations, protein expression and gene expression, to highlight the cases in which systematic characterization of the whole proteome and phosphoproteome can uncover insights that are undetected with RNA sequencing.

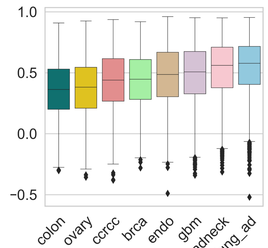
The analysis described below applies RNA-protein-phosphorylation comparisons based on clinical cancer datasets. We make use of the large amount of data generated by the Clinical Proteomic Tumor Analysis Consortium (CPTAC)[1], which generates protein, mRNA and unique phosphorylations data from the exact same samples.

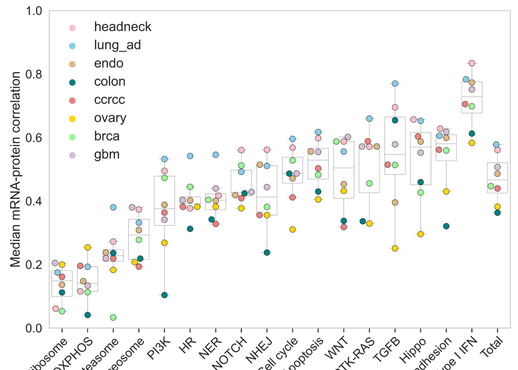


Transcriptomics | Proteomics | Phosphoproteomics

Gene expression is a limited predictor of protein expression and protein function

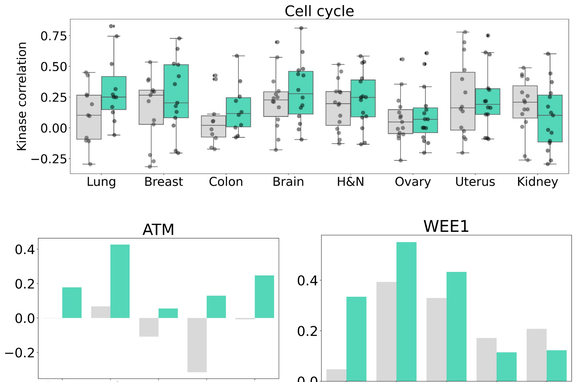
The average Spearman rank correlation between RNA and protein expression ranges from 0.4 to 0.6 in different tumor types





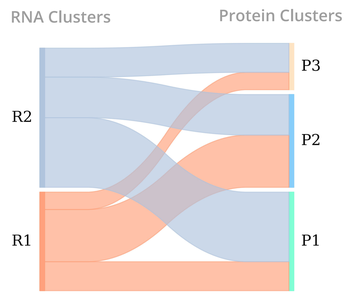
Focusing on kinase-enriched pathways (cell cycle and DNA damage repair [DDR]), shows that the **correlation between kinase protein expression and kinase activity is consistently higher than the correlation between kinase RNA expression and activity.**

RNA-kinase correlation
Protein-kinase correlation



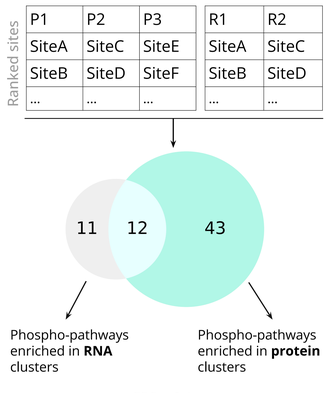
Differences between RNA and protein-based classification of ovarian tumors are reflected in phosphorylation-enriched pathways

Ovarian tumor samples[4] separated into two clusters based on RNA, and three clusters based on protein

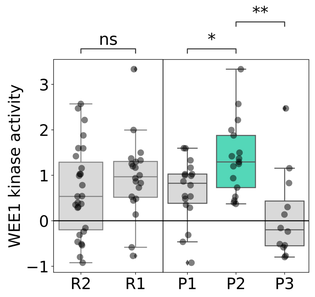


Each of the RNA-based clusters separated into each of the three protein-based clusters with **low concordance**

Protein-based clusters are significantly enriched for more phospho-pathways than RNA-based clusters

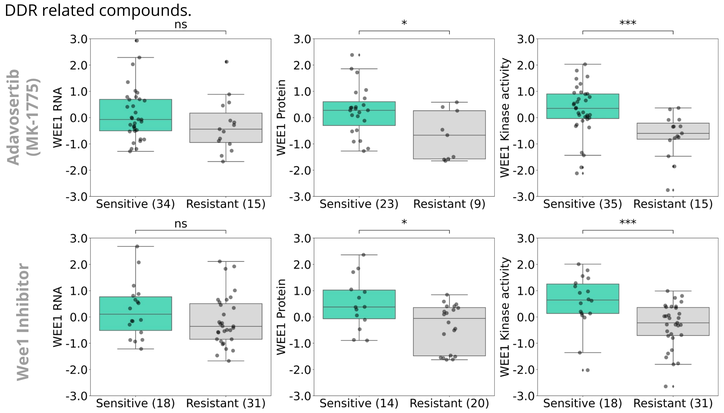


Analyzing kinase activity in the clusters of each classification showed that WEE1 is highly active in P2, whereas no such difference was found in RNA clusters



Kinase activity predicts response better than RNA/protein expression

To further examine the contexts in which protein expression and/or function are clinically relevant, we utilized publicly available proteomics (NCI-60)[6] and drug screens[3] and looked for associations between drug sensitivity and RNA/protein/kinase levels specifically in cell cycle and DDR related compounds.



For both WEE1 inhibitors, kinase activity was significantly associated with drug sensitivity, while protein RNA expression were either weakly associated or insignificant

Summary and future steps

- We show here the limited utility of RNA to predict protein expression and function.
- Clustering differences in transcriptomics and proteomics are manifested in the enrichment of kinase-driven pathways, enabling potential discovery of subpopulations sensitive to targeted treatment.
- Indeed in the preclinical setting, kinase activity predicts response better than RNA/protein expression, specifically in WEE1 inhibition.
- These analyses show the the critical role of proteomics and phosphoproteomics in tumor characterization, and highlight the potential of proteomic and phosphoproteomic data to create novel predictive response biomarkers. In the future, we will apply these analyses to additional cell cycle/DDR targets and validate using both xenograft models and clinical samples.

References

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