Integrated analysis of transcriptomics and kinase activity data for better characterization of cancer models

#LB060

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Introduction

Background:

Quantitative measurements of transcripts and proteins only provide information about the basal state of a biological system, in contrast, functional proteomics are essential to investigate the active state of regulatory networks. Thus, the application of "multi-omics" strategies and their integration could improve understanding of the mechanisms underlying cancer.

Aim of the study:

Integration of transcriptomics (RNAseq) and kinomics (Pamgene kinase activity) data for :

- Better characterization of various cancer models.
- Improve identification of new cell signaling targets

Method:

- Kinase activity was profiled using Pamchip® Technology (Fig.1).
- RNAseq was performed on an Illumina NovaSeq platform.
- Analysis was performed on 63 Patient Derived Xenografts (PDX) from six cancer types (Fig.2).
- Kinase signaling-specific genes (n=2932) were selected from the Reactome database Signal Transduction Pathway (n=2560) and additional kinases (n=372) represented on Pamchip.

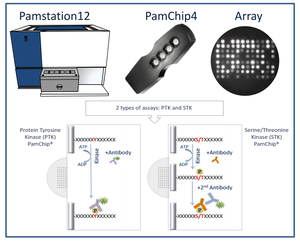

Fig.1. Kinase activity profiling on PamChip® microarrays

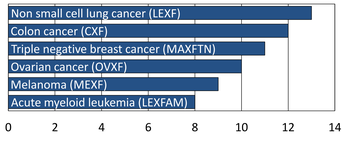

Fig.2. Sample distribution across six cancer types

Multi-Omics Factor Analysis (MOFA)

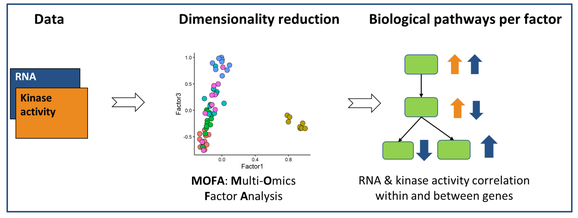

Fig.3. Workflow for integration of RNAseq and kinase activity data. MOFA implements dimensionality reduction to find factors (i.e. correlated RNAs and phosphosites) capturing variability shared across data sources. For features within a factor, pathways were analysed using Metascape.

Kinase signaling identifies PDX models cluster

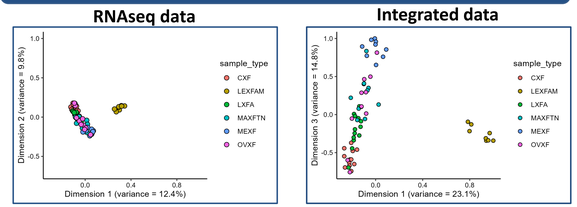

Fig.4. Principal component analysis (*left*) using only RNAseq data and MOFA analysis (*right*) using integrated data describing variation between different PDX models.

Integrated data identifies new pathways

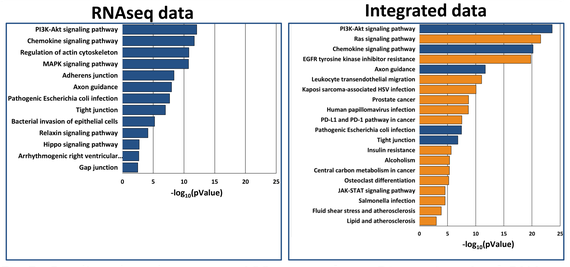

Fig.5. Predicted pathways on 100 genes from Dimension 1 of RNAseq data (*left*) or 50 genes and 50 phosphosites from Dimension 1 of integrated data *(right)*. New pathways in integrated data are highlighted.

Integrated data enrich pathway analysis

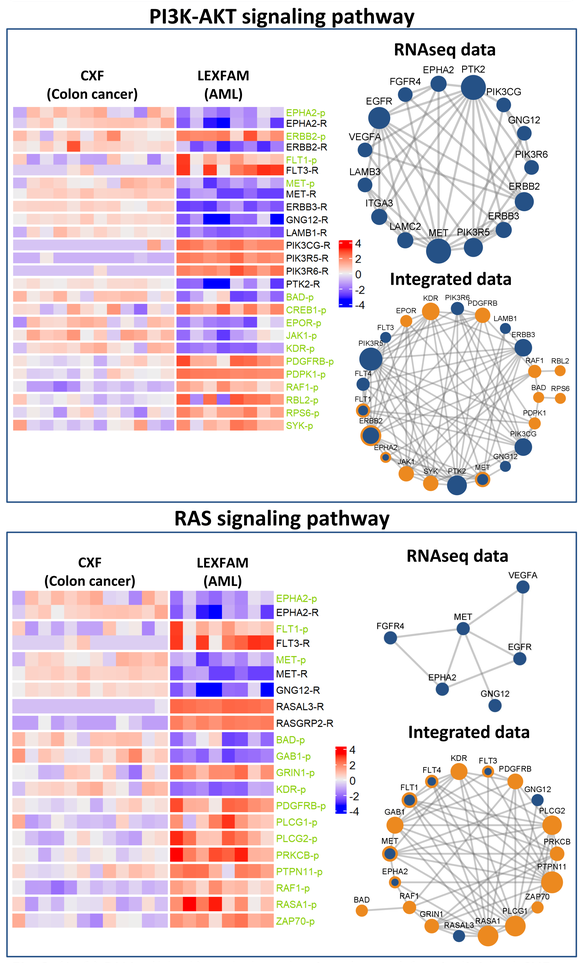

Fig.6. (*Left*) RNAs (*black*) and phosphosites (*green*) for individual CXF or LEXFAM PDX model. CXF is shown as representative of 5 tumor clustering separately from LEXFAM in Fig.4. (*Right*) Protein-protein interaction for PI3K-AKT (*top*) and RAS (*bottom*) signaling pathway.

Integrated data helps to select PDX models

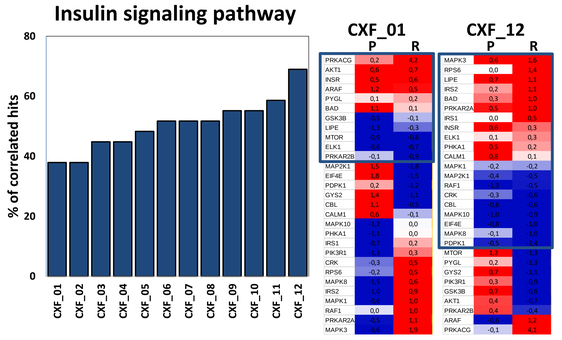

Fig.7. (A) Percentage correlation of 29 RNAs and phosphosites from insulin signaling pathway in 12 CXF (Colon cancer) PDX models. Samples are ranked based on correlation score. (B) Heat map depicting signals of correlated (box) phosphosites (P) and RNAs (R) in two CXF PDX model.

Conclusions

- Kinase related signaling genes capture variation in different PDX tumor models.
- Compared to RNAseq alone, integrated RNAseq-phosphosite data:
  - Explain more variance between PDX tumor models.
  - Enhances statistical score of biological pathways.
  - Enrich for additional relevant pathways
- High correlation between two datasets improves target characterization within a tumor group and enables selection of relevant animal models addressing specific research questions.

Integration of the active kinome and RNAseq data strengthens biological interpretation and identifies hidden targets and pathways.

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