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Type	Oral communication
Session	Multi-Omics
Title	Integrating transcriptomic and phosphoproteomic data to discover dysregulated transcriptional networks in lung cancer
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Motivation

Transcription factors (TF) hold a primary role in tumorigenesis, as they are central regulators for the activity of the large and complex expression programs that ultimately govern cell fate. Accordingly, multiple studies have sought to characterize their role in different cancer types with the goal of deriving prognostic and diagnostic biomarkers and new targets for therapeutic intervention. Given this critical role, the inference of TF activity from transcriptomic data is an active area of research. Here we developed a novel approach that integrates genomic, transcriptomic and phosphoproteomic data to provide an integrated characterization of the activity of TF and the modulation of their upstream and downstream signaling networks. Our methodology was applied to a large dataset of lung adenocarcinoma patients with the goal of identifying correlates of patient survival.

Methods

We leveraged expression data from patient samples to calculate a patient-specific activity score for 1010 human TFs. This data was enriched with genomic information related to the binding of TFs to super-enhancers to distinguish direct vs indirect targets of each TFs, thus identifying smaller regulatory networks that are more directly indicative of TF activity. We then employed Kaplan-Meier survival analysis to investigate the power of TF activity measures in predicting patient survival. Finally, the role of signaling networks in modulating TF function was investigated by using LASSO regression to identify phosphorylation events that are predictive of TF activity.

Results

Starting from 1010 TFs, we selected 34 TFs with a dysregulated activity in LUAD patients. The integration of genomic and transcriptomic data identified ERG and FOXO3 as key regulators whose activity is predictive of patient survival in lung adenocarcinoma. In order to link the activity of these TFs to upstream and downstream regulatory networks, we leveraged phosphoproteomic data obtained on the same samples and used LASSO regression to identify phosphorylation events that are predictive of TF activity. This analysis again identified ERG as a key regulator for which the signaling state upstream and downstream was associated with patient survival. Finally, by combining the gene expression- and phosphoproteomics-derived measures of the activity of ERG and its regulatory network we were able to identify, with high significance, a subgroup of patients with markedly worse outcomes. ERG is a transcription factor implicated in several processes, including angiogenesis and cell proliferation. This TF is also well known in prostate cancer where its overexpression is associated with disease progression, here we highlight its prognostic role in lung adenocarcinoma patients.

Info

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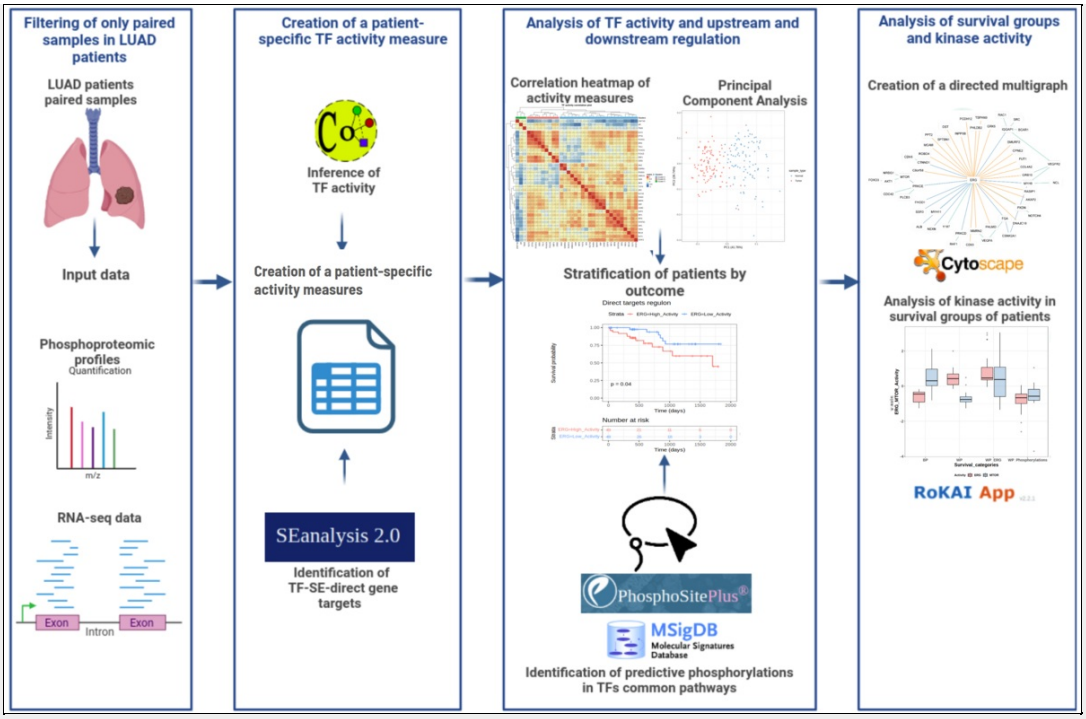
Figure



Availability https://docs.google.com/document/d/13Z8kfZBL92sSPji1ABn6njwNvC7toOvbwqiCIxKny64/edit?usp=sharing

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Summary

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