MoBaS on Phosphorylation Data

Marzieh Ayati
Case Western Reserve
University
10900 Euclid Ave
Cleveland, OH
mxa401@case.edu

Goutham Narla
Case Western Reserve
University
10900 Euclid Ave
Cleveland, OH
gxn71@case.edu

Danica Wiredja
Case Western Reserve
University
10900 Euclid Ave
Cleveland, OH
ddw34@case.edu

Mark R Chance
Case Western Reserve
University
10900 Euclid Ave
Cleveland, OH
mrc16@case.edu

Daniela Schlatter
Case Western Reserve
University
10900 Euclid Ave
Cleveland, OH
dms73@case.edu

Mehmet Koyuturk
Case Western Reserve
University
10900 Euclid Ave
Cleveland, OH
mxk331@case.edu

ABSTRACT

Although advances in high-throughput omics technologies revolutionized our understanding of the genomic underpinnings of cancer, there are still many challenges in understanding how patients with common driver mutations may display diverging phosphoproteomic responses to the same treatment. Thus, an examination of the signaling landscape will provide essential molecular information for modeling personalized patient treatment design. However, integrative bioinformatics approaches to identify phosphoproteomics-based molecular states are in their infancy. To address this challenge, we integrated several bioinformatics tools to compare and contrast the drug-induced global signaling alterations of two KRAS mutated non-small cell lung cancer (NSCLC) cell lines, A549 and H358, treated with a novel activator of the tumor suppressor Protein Phosphatase 2A (PP2A) versus DMSO control.

To identify protein subnetworks that are enriched in differentially phosphorylated proteins, we use our algorithm MoBaS which is designed to identify protein subnetworks that are enriched in disease-associated genomic variants identified by genome-wide association studies (GWAS). MoBaS takes as input a PPI network and a score for each protein indicating the protein's association with the phenotype of interest. It then identifies protein subnetworks that are (i) composed of densely interacting proteins, and (ii) enriched in proteins with high scores. MoBaS also assesses the statistical significance of the identified subnetworks using permutation tests that enable multiple hypothesis testing. Subsequently, we do kinase enrichment within the statistical significant modules and find Aurora KB as a key kinase differentially regulated between the two cell lines in response to our compound. Further corroborating this finding, Au-

ror KB was downregulated at the protein and mRNA levels with our treatment in A549 but not in H358. Ultimately, our approach models the diverging protein-level drug response across two similar cell lines representing NSCLC patients. Such phosphoproteomic information will potentially inform the optimal therapy regimen for each individual.

Categories and Subject Descriptors

J.3 [Life and Medical Sciences]: Biology and genetics

General Terms

Algorithms, Design, Experimentation

Keywords

Phosphoproteomics, protein protein interaction networks, functional modules, statistical significance, network analysis

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