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Proteomic Analysis Identifies RhoA as a Novel Therapeutic Target for Peritoneal Fibrosis

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Objectives : Peritoneal dialysis (PD) is an essential treatment for patients with chronic kidney disease (CKD). However, peritoneal fibrosis (PF), a common complication of PD, significantly impairs its efficacy and increases the risk of peritonitis, cardiovascular diseases, and the progression of CKD. Here, we analyzed the proteome of human peritoneal mesothelial cells (hPMCs) from CKD patients and conducted drug connectivity analyses to identify key biomolecules linked to PF, particularly focusing on the RhoA protein.
Methods : hPMCs were isolated from PD effluent and were treated with 2 ng/mL rTGF-β for 48 hours to induce fibrosis. TMT tag-based quantitative proteomic analysis was conducted to investigate the global proteome profile of hPMCs. Identified differentially expressed proteins (DEPs) were subjected to pathway analysis using the KEGG Database and drug connectivity analysis using the Proteomic Atlas for Small Molecule Perturbagens Database to identify potential drug targets.
Results : A total of 8,961 proteins were quantified in hPMCs. Treatment with rTGF-β induced a significant increase in the expression of key extracellular matrix proteins, including FN1, COL1A1, and TAGLN. DEPs were further selected based on their increased expression in response to rTGF-β treatment for drug connectivity analysis. Potential therapeutic candidates were identified, including inhibitors of RhoA, PDGFR, and tyrosine kinase, which may counteract the gene expression patterns associated with PF. Notably, RhoA, an important GTPase that regulates myofibroblast differentiation, was found to be highly expressed in hPMCs, highlighting its potential as a therapeutic target for PF.
Conclusions : These findings suggest that targeting RHOA, along with other identified inhibitors, could offer promising therapeutic strategies for mitigating PF.

HPMC_Fig1.png


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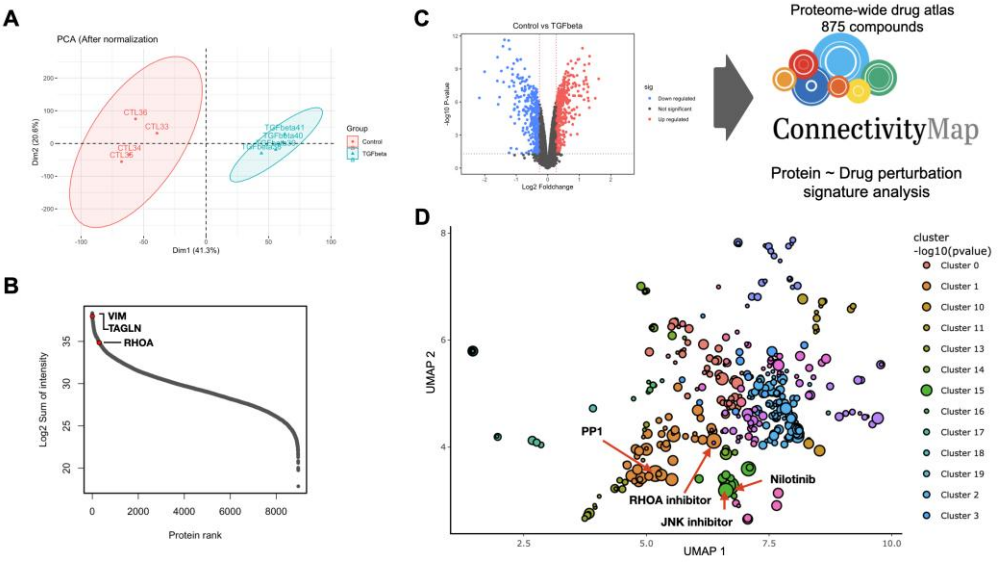
A
PCA (After normalization
Dim1 (41.3%)
Dim2 (20.6%)
Group
Control
TGFbeta
B
VIM
TAGLN
RHOA
Log2 Sum of Intensity
Protein rank
C
Control vs TGFbeta
Log2 Foldchange
-log10 P-value
sig
Down regulated
Not significant
Up regulated
Proteome-wide drug atlas
875 compounds
ConnectivityMap
Protein ~ Drug perturbation
signature analysis
D
UMAP 1
UMAP 2
cluster
-log10(pvalue)
Cluster 0
Cluster 1
Cluster 10
Cluster 11
Cluster 13
Cluster 14
Cluster 15
Cluster 16
Cluster 17
Cluster 18
Cluster 19
Cluster 2
Cluster 3
PP1
RHOA inhibitor
JNK inhibitor
Nilotinib