The 4th Iranian Conference on Systems Biology

Decoding linagliptin protective effects on kidney and cardio by investigating its transcription factors-microRNAs -target genes regulatory network

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Abstract

✓ Linagliptin is a novel antidiabetic drug from the dipeptidyl peptidase four inhibitors (DPP4I) class.

✓ It shows protective effects on cardiac and kidney damage, which are the most important complications of diabetes mellitus type2.

✓ So, we intend to unveil molecular mechanisms of linagliptin's protective effects by a systems biology approach.

Keywords: linagliptin, diabetes mellitus type2, regulatory network , motif , transcription factor, microRNA

Introduction

✓ About one in 11 adults worldwide now have diabetes mellitus , 90% of whom have type 2 diabetes mellitus (T2DM).

✓ Long-term microvascular and macrovascular complications of diabetes develop gradually. They can eventually be disabling or even life-threatening.

✓ linagliptin not only has anti diabetic effects but also ameliorates it's complications. so we intend to investigate it's molecular interactions by bioinformatic approach.

Materials and Methods

Searching for high throughput data related to linagliptin in GEO database, Array Express, and published works:
- 1GSE found (GSE98226)
- 2 articles found with high throughput data (peptide mapping, RNA sequencing)

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Analyzing data to detect differentially expressed genes (Divided into increased expression genes (IEG) and decreased expression genes (DEG))

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Prediction of regulatory relationships:
TRRUST & TRANSFAC databases: TF → gene
miRTarBase & miRecords databases: miR → gene
miRTarBase database: miR → TF
TransmiR database: TF → miR

↓

Gene Regulatory Network (GRN) construction by Cytoscape Detection of significant **3-node regulatory motifs** by FANMOD and creation of sub-networks

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Enrichment analysis by DAVID (Gene ontology and KEGG pathway) | **Selecting important genes** (Hub, botteleneck, and motifs)

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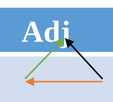
Verification of the most important genes, biological processes and pathways by experimental studies

Results

✓ Among 3-node regulatory motifs, a feed-forward loop scored significantly (p-value<0.01 and z-score>2) in each network. (black arrow is TFs regulate genes, green arrow is miRs suppress genes, red arrow is TFs regulate miRs and blue arrow is miRs suppress TFs)

	Z-Score	P-Value	Adj
IEG	2.8584	0.008	
DEG	3.117	0.001	

✓ Enrichment of subnetwork genes showed biological processes and pathways, that are related to the molecular pathology of T2DM, cardiovascular disease, and kidney dysfunction.

BPs of IEG	Localization, cellular localization, protein localization, anatomical structure morphogenesis, establishment of protein localization, vesicle-mediated transport, intracellular transport , extrinsic apoptotic signaling pathway
BPs of DEG	tissue development, cell death, apoptotic process, localization, locomotion, cellular component organization, cell motility, system development
Pathways of IEG	Rap1 signaling pathway, Platelet activation, Hippo signaling pathway
Pathways of DEG	PI3K-Akt signaling pathway, FoxO signaling pathway, Apoptosis, cAMP signaling pathway, Focal adhesion, TNF signaling pathway, Insulin resistance , AMPK signaling pathway, Insulin signaling pathway, circadian rhythm

Discussion, Conclusion and Suggestions

✓Exploring related experimental articles verified that seven top genes of increased expression genes subnetwork (including SERPINE1, HNRNPA2B1, COL1A1, IL1B, CXCL10, GCG and GABPA) and five top genes of decreased expression genes subnetwork (including SPP1, ATM, IRS1, APOB and CASP3); which are all related to these top biological processes and KEGG pathways; have previously been reported to play roles in mentioned pathologies.

✓Topological analysis of two merged TF-miRNA-gene regulatory networks showed that a number of genes (including SPP1, RELA, STAT3, POU2F1, SMAD2, SERPINE1, GABPA) are among genes with the 5% top highest degree and between-ness centrality in the networks. we verified the majority of these top genes by other experimental studies related to Linagliptin effect or the mentioned pathologies.

✓Based on this ground we recommended the other genes available in the model for further investigation of their probable role in Linagliptin effect or the mentioned pathologies.

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