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Integrative systems biology approach prioritizes geldanamycin-HSP90AB1 as a common drug-target candidate in type 1 diabetes and multiple sclerosis

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Abstract

The aim of this study was to prioritize common targets and potential drugs for type 1 diabetes (T1D) and multiple sclerosis (MS) via systems biology approach. Differential expressed genes were integrated with protein-protein interactions (PPI) data. The centrality parameters of sub-networks were calculated. The interaction of drug-central nodes were investigated and docking analysis was performed. HSP90AB1 introduced as a more central node in the sub-networks of T1D and MS. The analysis of docked complex of geldanamycin-HSP90AB1 revealed binding affinities of -8.83 and -7.4 kcal/mol in AutoDock-4 and AutodockVina (RMSD 5.83 Å). This study emphasized on the importance of network-based drug-target prioritization.

Keywords: Systems biology, T1D, MS

Introduction

T1D and MS are classified as T cell-mediated autoimmune diseases [1]. Co-occurrence of MS and T1D has been reported in several studies [2]. Despite noticeable improvement in patients' survival and health, a cure for T1D and MS remains elusive. Paradigm shift from molecular understanding of biological resources into systems-based approach has provided new opportunity to develop novel drug strategies and showed the necessity of a consistent move from traditional pharmacology [3]. Network based gene expression profiling constructed by integrating multiple factors including disease genes, gene expression intensities and proteins network, which provided efficient strategy to discover therapeutic signatures. Here, We integrated transcriptome-interactome data to construct PPI networks in T1D and MS. Candidate drugs and targets were then prioritized from the analysis of central genes and drugs interactions. Docking analysis disclosed the interactions between candidate drug and target.

Materials and Methods

Two datasets (GSE9006 and GSE35296) corresponding to gene expression profiles of peripheral blood mononuclear cells (PBMCs) and pancreatic-β cells in T1D as well as one dataset (EMTAB-69) involving gene expression profiles of PBMCs and cerebrospinal fluid (CSF) for MS were analyzed. Packages of affy, genefilter and limma were retrieved from Bioconductor website in R environment for the analysis of these data. Human protein-protein interaction (PPI) network was constructed using four major IMEx public databases, IntAct, MINT, DIP and InnateDB. Differential expressed genes (DEGs) in each of tissue were integrated with PPI data and corresponding sub-networks were extracted by Cytoscape software. Centrality parameters of sub-networks were calculated by CeNtiBin software. Common more central genes were manually screened in DrugBank database (version 5.4.1) to find potential drugs. Docking analysis was performed for HSP90AB1 as a target gene and geldanamycine to assess their interactions at atomic level. The crystal structure of HSP90AB1 (PDB ID: 1UYM) was used for docking analysis. AutoDock software and AutoDockVina in PyRx Virtual Screening tool were used for molecular docking analysis.

Results

The number of DEGs were 2466 genes ($P < 0.05$) in PBMCs, 3068 genes in pancreatic β-cells (FDR < 0.05) in T1D as well as 1,163 DEGs genes (FDR<0.1) in PBMCs and 3,062 genes (FDR < 0.05) in CSF in MS. Constructed sub-networks involved 949 nodes, 1776 edges in PBMCs and 1358 nodes, 3505 edges in pancreatic β-cells in T1D as well as 483 nodes, 941 edges in PBMCs and 1440 nodes, 3500 edges in CSF in MS. Central nodes were determined. HSP90AB1 introduced as a more central node in pancreatic β-cells PPI network in T1D with the following measurements: degree= 112, Betweenness centrality=0.141, Closeness centrality=0.368, Centroid value=64, Eigen vector=0.287. Besides, HSP90AB1 was the second more central node in PBMCs PPI network in MS with the following measurements: degree= 49, Betweenness centrality=0.171, Closeness centrality=0.374, Centroid value=55, Eigen vector=0.287. Drug-target analysis showed geldanamycin targets HSP90AB1 gene. Geldanamycin was studied for the treatment of experimental models of T1D and MS. Finally, the docking analysis of geldanamycin-HSP90AB1 complex resulted in 150 conformations docked and the conformation corresponding to the lowest binding energy was selected as the most probable binding conformation. The analysis of binding site residues lying within 4 Å distance of ligand indicated that the drug was surrounded by both hydrophobic and hydrophilic residues. The docked complex of geldanamycin -HSP90AB1 showed binding affinities of -8.83 and -7.4 kcal/mol in AutoDock-4 and AutodockVina (RMSD 5.83 Å) respectively, which is bound with alpha helix residues such as GLY-137 (3.105 Å) and PHE-138 (3.06537 Å), Table 1 and Fig.1.

Table 1. Binding free energy of geldanamycin–HSP90AB1 complex and the corresponding interaction energies.

Drug	Receptor	AutoDock-4 (Kcal/mole)	Autodock Vina (Kcal/mole)	RMSD in Å	Hydrogen bonding interactions		
					Interacting Residues	Distance (Å)	Angle (Degree)
Geldanamycin	HSP90AB1	-8.83	-7.4	5.838	GLY-137	3.105	
					PHE-138	3.065	
Residues (4 Å distances)	GLE-47,LEU-48,ASN-51SER-52,ASP-54,ALA-55,LEU-56,LYS-58,ILE-96,GLY-97,MET-98,THR-98,ASP-102,ASN-106,PHE-134,GLY-135,VAL-136,GLY-137,HIS-154						

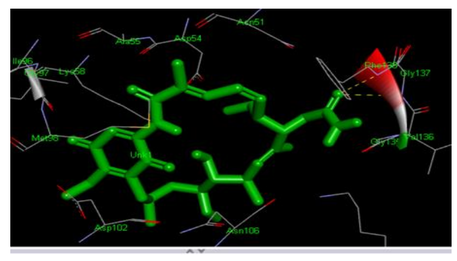

Figure1. Molecular docking complex of geldanamycin-HSP90AB1.

Discussion, Conclusion and Suggestions

Systems biology approach provide holistic view improved our understanding of disease mechanisms and introduce new way for discovery of novel drugs and repurposing of existing drugs. This study emphasized on the role of systems biology approach to reveal potential drug-target complexes in diseases. Our study prioritized drug (geldanamycin) that targets common key gene (HSP90AB1) in T1D and MS. Besides, the interaction of geldanamycin-HSP90AB1 at atomic level was more explored by docking analysis. Geldanamycin introduced as a HSP90AB1 inhibitor. HSP90 inhibitors improved hyperglycemia in the diabetic db/db mouse model [4]. Besides, the protective effects of geldanamycin's derivatives has been reported such as anti-inflammatory and direct neuroprotective effects in MS experimental model [5]. In overall, network-based analysis would give a new thought to prioritize and discover more effective drug-targets for treatment of patients with T1D /MS.

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