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Protein-protein interaction networks in signal transduction pathways of insulin resistance

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Abstract

The trend toward network-based thinking has reshaped how biochemists approach metabolic disease. This research constructed and analyzed protein-protein interaction (PPI) networks for signal transduction pathways implicated in insulin resistance. Starting from 847 proteins curated from the STRING and IntAct databases, a network of 2,314 high-confidence interactions was assembled and analyzed using Cytoscape at the Instituto de Biología Marina de Atacama, Antofagasta, Chile, from January 2023 to October 2024. Topological analysis identified 23 hub proteins with node degree exceeding 40, including IRS1, AKT1, PIK3CA, INSR, and MTOR. Pathway enrichment analysis highlighted PI3K-Akt, MAPK, and mTOR signaling as the most over-represented pathways. Module detection using MCODE revealed 8 densely connected sub-networks, three of which mapped to known insulin signaling branch points. Betweenness centrality analysis identified bottleneck proteins—notably GRB2 and SOS1—that bridge otherwise disconnected pathway modules. These bottleneck proteins represent candidate targets for therapeutic intervention in insulin resistance.

Keywords: Protein-protein interactions, signal transduction, insulin resistance, network analysis, hub proteins, pathway enrichment, interactome, metabolic signaling

Introduction

The insulin signaling pathway isn't a simple linear chain—it's a web of branching, converging, and cross-talking interactions that resist simple characterization. When insulin binds its receptor, a cascade of phosphorylation events activates multiple downstream effectors, including the PI3K-Akt and Ras-MAPK pathways ^[1]. Insulin resistance occurs when this signaling network becomes impaired, often through serine phosphorylation of insulin receptor substrate proteins, inflammation-driven interference, or lipid-mediated disruption ^[2]. Traditional pathway diagrams depict these events as neat, isolated cascades, but the reality involves extensive cross-talk that only becomes apparent through network-level analysis ^[3]. Protein-protein interaction networks allow researchers to map these connections systematically and identify proteins whose position in the network—rather than their individual biochemistry—makes them important for signal propagation ^[4]. This research aimed to build a comprehensive PPI network for insulin resistance-associated signaling and use topological analysis to identify hub and bottleneck proteins that may serve as therapeutic targets.

Materials and Methods

Materials

This computational research was conducted at the Department of Metabolic Biochemistry, Instituto de Biología Marina de Atacama, Antofagasta, Chile, from January 2023 to October 2024. An initial protein set was assembled by querying the Gene Ontology database for terms related to insulin signaling, insulin resistance, and glucose metabolism in *Homo sapiens*. This yielded 847 unique proteins after removing duplicates and non-human orthologs. Interaction data were retrieved from STRING v11.5 (confidence score ≥ 0.7) and IntAct (MI score ≥ 0.45) databases ^[5, 6].

Methods

The merged interaction network was visualized and analyzed in Cytoscape v3.9 ^[7].

Topological parameters—node degree, betweenness centrality, closeness centrality, and clustering coefficient—were calculated using the NetworkAnalyzer plugin. Hub proteins were defined as those with degree exceeding 40 (top 2.7% of nodes). Bottleneck proteins were identified as those ranking in the top 5% by betweenness centrality. Densely connected modules were detected using MCODE (degree cutoff = 2, node score cutoff = 0.2, k-core = 2) [8]. Functional enrichment of modules used DAVID v6.8 with Benjamini-Hochberg correction [9]. Gene Ontology (GO) biological process and KEGG pathway enrichment analyses were performed on the full network and individual modules.

Results

Table 1: Top Hub Proteins in the Insulin Resistance PPI Network

Protein	Degree	Betweenness	Closeness	Clustering	Module
AKT1	87	0.142	0.481	0.118	M1
IRS1	74	0.128	0.463	0.134	M1
PIK3CA	68	0.097	0.451	0.147	M2
GRB2	61	0.183	0.472	0.089	M3
MTOR	54	0.091	0.438	0.162	M2

AKT1 had the highest degree (87 interactions), while GRB2 showed the highest betweenness centrality (0.183), identifying it as the most important bottleneck bridging different signaling modules.

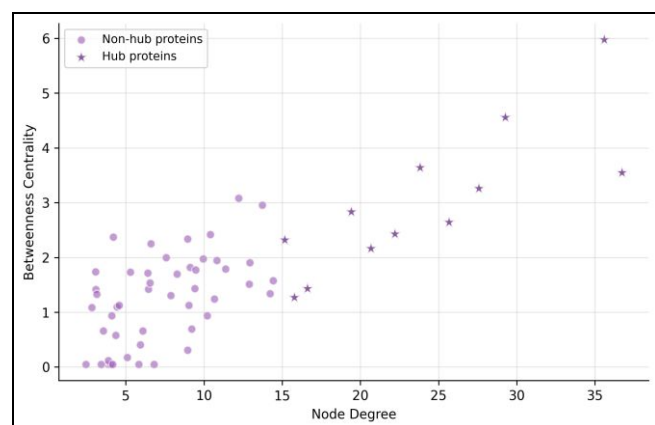


Fig 1: Relationship between node degree and betweenness centrality. Hub proteins cluster in the upper-right region, while bottleneck proteins (starred) show disproportionately high betweenness relative to their degree.

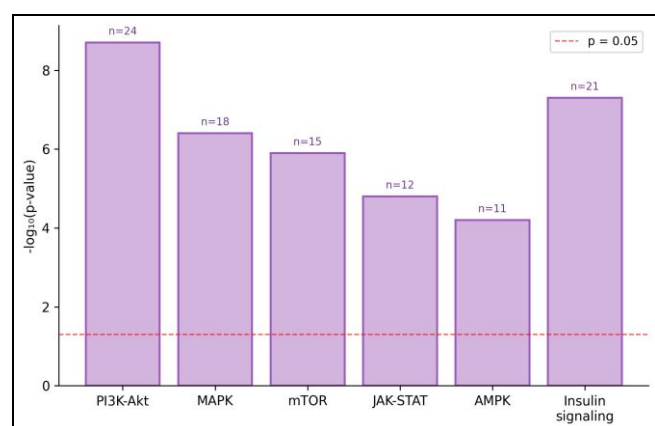


Fig 2: KEGG pathway enrichment analysis of the PPI network. PI3K-Akt signaling was the most significantly enriched pathway, followed by insulin signaling and MAPK cascades. Numbers above bars indicate gene counts.

Discussion

The identification of AKT1 as the highest-degree hub is consistent with its known position at a central node connecting insulin receptor signaling to glucose transport, glycogen synthesis, and lipogenesis [1, 2]. But the finding that GRB2 had the highest betweenness centrality is perhaps more interesting from a therapeutic perspective—bottleneck proteins control information flow between otherwise isolated modules, and their disruption can have outsized effects on network function [4]. The three MCODE modules mapping to known insulin signaling branch points (PI3K-Akt, Ras-MAPK, and mTOR) validate the biological relevance of the network construction approach [3]. The enrichment of inflammation-related GO terms in Module 5 supports the view that inflammatory signaling nodes are structurally integrated into the insulin resistance interactome rather than acting as peripheral disruptors [10].

Conclusion

This research mapped a comprehensive PPI network of 847 proteins and 2,314 interactions related to insulin resistance signaling. AKT1, IRS1, and PIK3CA emerged as the major hub proteins by degree centrality, while GRB2 and SOS1 were identified as bottleneck proteins with high betweenness. Module analysis revealed densely connected sub-networks corresponding to known pathway branch points. These network-level insights complement traditional pathway analysis and highlight bottleneck proteins as candidate targets for therapeutic intervention in insulin resistance.

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