

# SYSTEMATIC NETWORK CREATION FOR HUMAN INSULIN RECEPTOR SUBSTRATE-1 BY SYSTEMIC BIOLOGY TECHNIQUE

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## SUMMARY

*Metabolic actions of insulin are mediated by the insulin receptor/insulin receptor substrate (IRS)-1/phosphatidylinositol 3-kinase signaling pathway in insulin target organs including the liver, skeletal muscle and adipose tissue. To understand the actual pathway of IRS-1 is the scientists' hope for better understanding the disease mechanism. In this work, a systematic network creation for human insulin receptor substrate 1 by systemic biology technique was performed. According to this work, there are at least 9 genes directly related to IRS-1 gene. Of interest, the relation of diabetes to some identified genes can be seen. In addition, identified relation to some genes implies a correlation between IRS-1 and cancer. The systematic network of IRS-1 created in this study could provide useful data for further works in diabetic and oncologic medicine.*

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## INTRODUCTION

Type 2 diabetes mellitus is a major cause of morbidity and mortality worldwide, and the prevalence is set to increase dramatically over the coming decades (1). Understanding the metabolic pathways that lead to type 2 diabetes is therefore an important healthcare objective (1). The pathophysiology of type 2 diabetes is characterized by defects in insulin action and in insulin secretion (2). Dysregulated insulin signaling exacerbated by chronic hyperglycemia promotes a cohort of systemic disorders including dyslipidemia, hypertension, cardiovascular disease, and female infertility (3). Understanding the molecular basis of insulin resistance can prevent these disorders and their inevitable progression to type 2 diabetes (3). Metabolic actions of insulin are mediated by the insulin receptor/insulin receptor substrate (IRS)-1/phosphatidylinositol 3-kinase signaling pathway in insulin target organs including the liver, skeletal muscle and adipose tissue (2).

Initial attempts to unravel the molecular mechanism of insulin resistance have strongly suggested that a defect responsible for insulin resistance in the majority of patients lies at the postreceptor level of insulin signaling. Subsequent studies in insulin-resistant animal models and humans have consistently

demonstrated a reduced strength of insulin signaling *via* the IRS-1/PI 3-kinase pathway, resulting in diminished glucose uptake and utilization in insulin target tissues (4). A combination of both increased expression of p85alpha and increased serine phosphorylation of IRS-1 is needed to induce clinically apparent insulin resistance (4). Inflammatory molecules and lipid metabolites inhibit insulin signaling by stimulating a number of different serine kinases, which are responsible for serine phosphorylation of IRS-1 (5). To understand the actual pathway of IRS-1 is the scientists' hope for better understanding the disease mechanism.

In this work, a systematic network creation for human IRS-1 by systemic biology technique was performed. The manuscript describes the investigation of IRS-1 physiological involvement in intracellular pathways that may be relevant for type 2 diabetes mellitus and possibly other pathological conditions. The hypothesis of work is that there are a set of genes directly relating to IRS-1 gene, which can be presented as a systematic network. Online systemics tool as for detection of molecular networks was performed. This is an important field of research of paramount clinical importance, with great implications for public health.

## MATERIALS AND METHODS

This work makes use of systemic biology technique for creation of systematic network. Firstly, the sequence search for human IRS-1 from online database, PubMed (www.pubmed.com) was performed for validation of the existence of the molecule. Then, the search for molecular networks by the CellCircuits (www.cellcircuits.org) (6) method was performed. The input searching term can be by either gene or ontology term. Briefly, this tool is designed to bridge the gap between databases of individual pairwise molecular interactions and databases of validated pathways (6). This tool captures the output from an increasing number of approaches that screen molecular interaction networks to identify functional sub-networks based on their correspondence with expression or phenotypic data, their internal structure, or their conservation across species (6). A combination of gene ontology parameters from all identified

molecular networks was performed. All pathways are integrated into the finalized network by direct linkage matching. A finalized systematic network was then generated. To interpret the resultant network, a line in the diagram shows a confirmed relationship in gene function.

## RESULTS

Firstly, the human IRS-1 gene (Chromosome: 2; Location: 2q36) could be derived from Pubmed and used for further systemic biology study. According to CellCircuits, there were 8 molecular networks. A combination of gene ontology parameters from all identified molecular networks is shown in Table 1, and a finalized systematic network in Figure 1. The main backbone of the derived network is the connection between JAK2 (a main node with 4 satellites) and IRS1 (a main node with 11 satellites).

**Table 1. A combination of gene ontology parameters from all identified molecular networks**

Molecular function	Biological process
Receptor binding, signal transducer activity, receptor signaling protein activity, SH2 domain binding, transmembrane receptor protein tyrosine kinase signaling protein activity, insulin-like growth factor receptor binding, insulin receptor binding	Transmembrane receptor protein tyrosine kinase signaling pathway, signal transduction, enzyme linked receptor protein signaling pathway, insulin-like growth factor receptor signaling pathway, cell communication, insulin receptor signaling pathway, cell surface receptor linked signal transduction

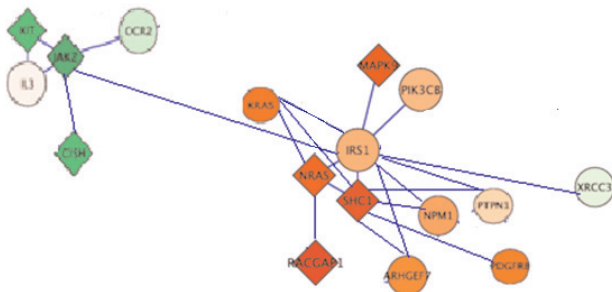
## DISCUSSION

Diabetes mellitus is a complex disorder that arises from various causes, including dysregulated glucose sensing and impaired insulin secretion, autoimmune-mediated beta-cell destruction (type 1), or insufficient compensation for peripheral insulin resistance (type 2) (3). Insulin resistance is a feature of a number of clinical disorders, including type 2 diabetes/glucose intolerance, obesity, dyslipidemia and hypertension, clustering in the so-called metabolic syndrome (5). IRS-1 plays a pivotal role in insulin signaling, whose function is impaired in subjects with insulin resistance.

Coordination of IRS-1 function is multi-faceted, involving phosphorylation of IRS-1 at multiple serine/threonine residues (7). This controls many aspects of IRS-1, including its interaction with the insulin receptor and subsequent tyrosine phosphorylation, as well as its subcellular distribution and targeting for degradation by the proteasome (7).

In this work, the author studied the systemic network for IRS-1 gene. After validation of IRS-1 gene in PubMed, the procedure used by the author was the systematic search of molecular interactions in a publicly available database, using the CellCircuits software ([www.cellcircuits.org](http://www.cellcircuits.org)). Focusing on the searching approach, the resulting models are available as images and matched by the names of proteins they contain or by their enriched biological functions (6). Then the author made an integration of the results in a single interaction diagram. According to this process, there are at least 9 genes directly related to IRS-1 gene (Fig. 1).

Figure 1. **Finalized systematic network.**



KIT = v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; IL3 = interleukin 3; CISH = cytokine inducible SH2-containing protein; OCR2 = origin recognition complex, subunit 2-like; JAK2 = Janus kinase 2; KRAS = v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; NRAS = neuroblastoma RAS viral (v-ras) oncogene homolog; SHC1 = Src homology 2 domain containing transforming protein 1; XRCC3 = X-ray repair complementing defective repair in Chinese hamster cells 3; NPM1 = nucleophosmin; ARHGEF7 = Rho guanine nucleotide exchange factor (GEF) 7; RACGAP1 = Rac GTPase activating protein 1; PTPN2 = protein tyrosine phosphatase, non-receptor type 2; PIK3CB = phosphoinositide-3-kinase, catalytic, beta polypeptide; MAPK9 = mitogen-activated protein kinase 9.

Of interest, the relation of diabetes to some identified genes can be seen. For example, Src homology 2 domain containing transforming protein 1 (SHC1) is proved to have strong correlation with defect of insulin signaling in rat model (8,9). On the other hand, the relation of diabetes to other identified genes (such as NPM1, ARHGEF7, etc.) still requires further

exploration. This can confirm the usefulness of systemics approach to detect the possible undiscovered correlation. In addition, identified relation to some genes implies the correlation between IRS-1 and cancer. In this paper, the analysis of gene function based on systemics approach was done and the detected relationship between IRS-1 and cancer could be identified, as shown in Figure 1. For more thorough description, the relations to v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KAS) and neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS) are good examples. Indeed, there are many recent reports indicating the correlation between IRS-1 and some cancers such as ovarian cancer (10) and colorectal cancer (11). However, it should be noted that genes involved in insulin/IGF-1 action might also be involved in cancer (e.g., PI3kinase because mutations were found in tumors). So, there is no further demonstration that IRS-1 would be involved in cancer more than PI3 kinase, IGF-1 receptor or IRS-2. Further verification is still recommended. Nevertheless, the systematic network of IRS-1 from this study could provide useful data for further works in diabetic and oncologic medicine.

This online tool employed in the study has been validated and used in many previous reports (12-15). It is accepted that the technique in this work could help reduce the time of search for correlation between the body of data and generate an overview network for holistic approach to a focused molecule. However, some limitations of this work have to be mentioned. This study is a bioinformatics based study making use of online tool and analysis of existing data in database. The data from undocumented clustering analysis, based on microarray of the same gene, cannot be included in the analysis. The originality of this work is not in reporting on the existing genes but in the creation of network by systemics approach. The identified systematic network has a biological significance based on manipulated data. This approach can be used in the research into other molecules such as IRS-2, which has been planned to do in the possible future study.

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