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Dysregulation of the TRIO-ELMO2-CSNK1G2 Axis Impairs GLUT4 Translocation in Type 2 Diabetes

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Abstract

This study investigates the roles of TRIO, ELMO2, and CSNK1G2 in type 2 diabetes via analyzing publicly available dataset of gene expression which obtain from insulin-resistant human skeletal muscle. Our analysis suggest a noticeable downregulation of the tested genes, which each of it encodes a protein participate in an vital cellular. Based on this study findings, we propose a regulatory mechanism referred to here as the TRIO\ELMO2\CSNK1G2 axis, which thought to be crucial for insulin-stimulated translocation of GLUT4 to the plasma membrane. The suggested suppression of this axis in diabetic patients may be the cause of defects in glucose uptake in such condition and through that contribute to the development of insulin resistance. These insights highlight a potentially novel therapeutic target for the treatment of type 2 diabetes.

Keywords: *Diabetes type2, TRIO, ELMO2, CSNK1G2, Pathway*

Introduction

Nutrient absorption and utilization begins with the ingestion of food as the first step in a long complicated digestion process. Food digestion act to reduces food macromolecules and convert it into a simpler biomolecules that the body can mobilize and store to be used during periods of nutrient deprivation or fasting. Insulin (a peptide hormone synthesized and secreted by pancreatic β-cells) play a major role in the process of regulation of nutrient uptake and storage. Insulin plays aan important role in stimulating nutrients

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transport of, particularly glucose, from the bloodstream into cell. Inside cells, glucose serve as substrates for process related to energy-generating and anabolism such as glycolysis, glycogenesis ,gluconeogenesis and lipogenesis. Diabetes mellitus is a condition that is usually related to dysfunction in insulin signaling.

Diabetes can be classified into two major types. Type 1 diabetes, often diagnosed in children, a condition that caused by autoimmune-mediated destruction of pancreatic β-cell resulting in acomplete insulin deficiency. This case require the use of insulin replacement therapy. On the other hand, in type 2 diabetes there is a peripheral insulin resistance as target cells are unable to appropriately respond to circulating insulin despite normal or even elevated levels of insulin. This resistance is thought to be due to some defects in insulin signaling pathways [1].

Insulin act through binding to a cell-surface receptor initiating another intracellular response through tyrosine kinase activity. Once the ligand bind to the cell surface receptor, the receptor go through auto-phosphorylation on specific tyrosine residues, which followed by the recruitment of phosphoinositide3-kinase (PI3K), a step which will stimuate the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2) to form phosphatidylinositol 3,4,5-trisphosphate (PIP3) [2,3]. PIP3 then recruits the serine/threonine kinase AKT which is also known as protein kinase B to the plasma membrane to be activated via phosphorylation. Phoephrylated AKT then dissociates from the membrane and act on several cytoplasmic and nuclear substrates, and by regulating the cellular response to insulin [2,3].

Regulation of glucose uptake in muscle and adipose tissue is considered one of the most important functions of insulin. Insulin act by translocating of GLUT4 (glucose transporter) from intracellular vesicles to the plasma membrane, which will facilitate glucose access into cells [4]. The molecular mechanisms that might explain the defect in GLUT4 trafficking in insulin resistance, especially in type 2 diabetes, still not understood completely, despite the intensive studying of insulin signaling, which highlights the importance of investigating the presence of other regulators for this pathway.

This study select three genes [TRIO, ELMO2, and CSNK1G2] as potential regulators in a novel signaling axis concerned with insulin-stimulated glucose uptake.

TRIO (Trio Rho Guanine Nucleotide Exchange Factor) is a gene that encodes a protein which act as a guanine nucleotide exchange factor (GEF), stimulating the exchange of guanine di-nucleotide to guanine tri-nucleotide on Rho family GTPases. It also mediates actin cytoskeleton reorganization, thereby influencing cellular growth and migration [4].

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ELMO2 (Engulfment and Cell Motility 2) encodes a protein that can interacts with the dedicator of cytokinesis 1 (DOCK1), also associated with apoptotic cells phagocytosis and in cytoskeletal remodeling and migration [5]. ELMO2 has also been noticed to play an important role in insulin-induced AKT membrane recruitment, proposing its important role in mediating the metabolic effect of insulin [6]. ELMO2 can regulates Rac1 activation via its interaction with DOCK, thus stimulating GLUT4 trafficking and glucose uptake. ELMO2 might act either in conjunction with, or downstream of TRIO in modulating Rac1-dependent processes.

CSNK1G2 (Casein Kinase 1 Gamma 2) can encodes serine/threonine kinase which participate in a wide range of cellular processes, such as circadian rhythm regulation, Wnt signaling pathway, and possibly desensitization of insulin receptor [5]. CSNK1G2 direct role in insulin signaling is less well defined, however, it may effect vesicle trafficking and endocytosis, which are necessary for the recycling and membrane action of the insulin-responsive transporters like GLUT4.

The current study hypothesized a signaling pathway connecting the functions of three genes [TRIO, ELMO2, and CSNK1G2]. In this hypothesized model, TRIO stimulate Rac1 activation, which can lead to remodeling of actin cytoskeleton. In addition, ELMO2, which is known to interact with DOCK proteins, lead to amplifying Rac1 signaling and participating in AKT recruitment to the plasma membrane. Also, CSNK1G2 through its effect on downstream kinases or vesicular trafficking machinery, this collectively can facilitate GLUT4 translocation and improving cellular uptake of glucose. The characterization and identification of this suggested axis could shed light on previously unrecognized mechanisms contributing to insulin resistance and may offer novel therapeutic targets for the management of type 2 diabetes.

Materials and Methods

2.1. Data Source and Preprocessing

Gene expression data used for this study were taken from the NCBI Gene Expression Omnibus (GEO), with the accession number GDS162, under the title [Type 2 diabetes and insulin resistance (Hu35k-D)]. The dataset contain expression profiles which were obtained from pooled vastus lateralis muscle samples of insulin-resistant and insulin-sensitive, non-diabetic, obese, Pima Indian individuals. The study was originally done by

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Yang et al. (2002), who used the Affymetrix Human 35K SubD Array (platform ID: GPL101) for the transcriptomic analysis of his data [7].

2.2. Gene Selection and Analysis

Three genes (TRIO, ELMO2, and CSNK1G2) were selected from the gene expression dataset due to their well-known roles in cytoskeletal reorganization, vesicular transport pathways directly linked to GLUT4 translocation and Rac1-mediated signaling. The expression levels of the three genes were compared between insulin-resistant and insulin-sensitive groups to examine the presence of statistically significant differential expression.

2.3. Pathway Integration and Hypothesis Generation

Correlation analyses were done to examine a potential relationships between the selected genes in the study. The results were presented in heatmaps and cluster plots. DAVID and the KEGG pathway database were used for pathway integration and functional annotation. The result obtained from these analytical pathways help to formulate a hypothetical regulatory cascade suggesting that TRIO can activates Rac1, originating cytoskeletal remodeling which also modulated furtherly by ELMO2 by interaction with DOCK proteins. The downstream gene, CSNK1G2 is suggested to effect GLUT4 mobilization and vesicle trafficking, which can collectively stimulating glucose uptake [8,9].

2.4. Statistical Analysis

Differential gene expression between studied groups was evaluated by t-test using GEO2R online tool. Hochberg's False Discovery Rate (FDR) and Benjamini for multiple comparisons correction, adjusted p-values (q-values) ≤ 0.05 was considered statistically significant. A fold-change threshold of ±2.5 (equivalent to log2 fold-change ≥ 1.32 or ≤ -1.32) was also used to detect genes with meaningful expression differences. Genes which was able to meet the selected criteria [fold-change cut-off (±2.5) and statistical significance (q ≤ 0.05)] were considered differentially expressed genes.

Results and Discussion

3.1. Gene Expression Findings

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The analysis done in this study showed that TRIO, ELMO2, and CSNK1G2 were consistently downregulated in insulin-resistant comparing to insulin-sensitive individuals. These genes encode proteins with complementary roles in the regulation of GLUT4 translocation, and together constitute what we propose as a novel TRIO–ELMO2–CSNK1G2 regulatory axis. TRIO, involved in actin cytoskeleton reorganization, likely provides structural support for the trafficking of GLUT4-containing vesicles. ELMO2 functions through Rac1-mediated signaling, regulating the actin dynamics essential for vesicle movement. CSNK1G2 appears to contribute to vesicle trafficking and membrane fusion, ensuring precise delivery of GLUT4 to the cell surface. The integrated action of these proteins is hypothesized to be critical for effective GLUT4 translocation in response to insulin stimulation, and their reduced expression may contribute to impaired glucose uptake characteristic of insulin resistance (Table 1-3, Figures 1-3 to 3–3).

Table 1-3 Significantly Downregulated Genes Identified from Expression Profiling of Insulin-Sensitive Muscle Tissue

Probe ID	adj. P-Value	P-Value	t-Statistic	B-Statistic	Log FC	Gene Symbol	Gene Description
RC_AA191348_at	0.0086	0.008609	-3.17	-4.43	-1.137	**TRIO**	Trio Rho guanine nucleotide exchange factor
RC_AA278754_at	0.0268	0.026776	-2.55	-4.47	-0.906	**ELMO2**	Engulfment and cell motility 2
RC_AA609691_at	0.0487	0.048658	-2.21	-4.50	-0.803	**CSNK1G2**	Casein kinase 1 gamma 2

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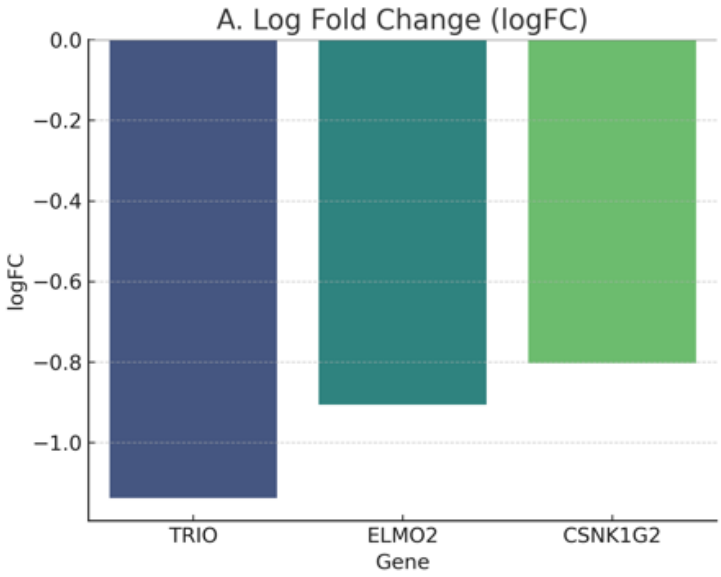

Figure 1-3 Downregulation of Key Genes in Insulin-Sensitive Muscle Samples

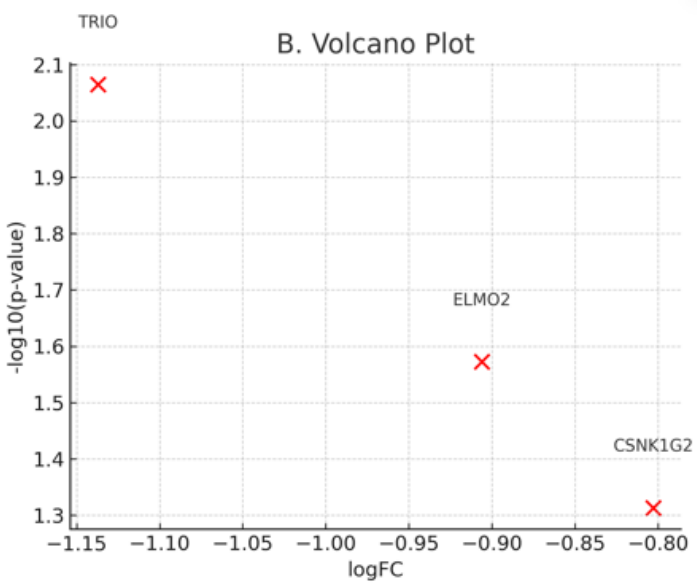

Figure 2-3 Volcano Plot Highlighting Differentially Expressed Genes

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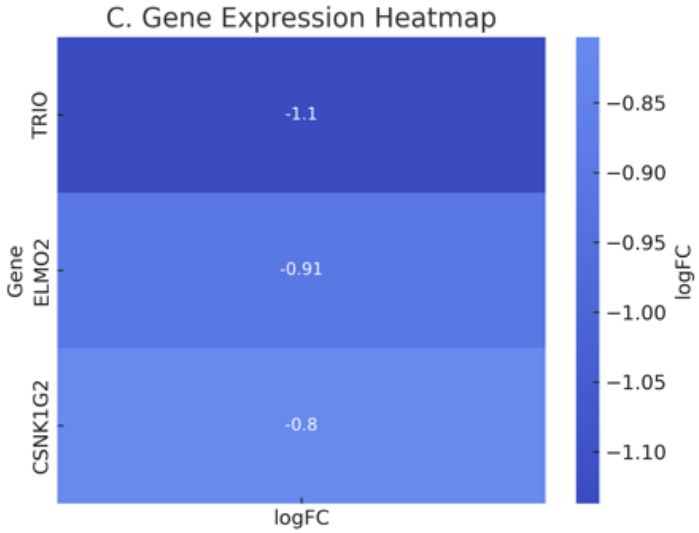

Figure 3-3 Heatmap illustrating the log fold change (logFC) of significantly downregulated genes in insulin-sensitive muscle samples. Color intensity represents the degree of downregulation, with blue indicating lower expression relative to baseline.

Discussion

Gene expression analysis illustrates the downregulation of TRIO, ELMO2, and CSNK1G2 in insulin-resistant samples. Such downregulation supports malfunction of the cellular machinery needed for the uptake of glucose stimulated by insulin. More specifically, low expression levels of TRIO and ELMO2 indicate problems with cytoskeleton remodeling and Rac1 signaling, vital aspects for GLUT4 translocation to the cell surface. At the same time, downregulation of CSNK1G2 may indicate an associated impairment in vesicle trafficking, the pathway through which GLUT4 reaches the plasma membrane. Results, therefore, indicate that the observed insulin resistance is most probably a cumulative outcome from impaired cytoskeletal dynamics plus attenuated Rac1 signaling plus impaired vesicle trafficking finally culminating in reduced GLUT4 translocation.

The work picks up general lowering of TRIO, ELMO2, and CSNK1G2 gene expression in insulin-weak vastus lateralis muscle samples against insulin-strong controls, which will possibly disrupting some of the important biological pathways that allow normally insulin to properly work and maintain balanced blood sugar levels in type 2 diabetes.

The genes which have been downregulated are in agreement with the earlier findings that faulty gene expression and protein function are characteristics of insulin resistance. For

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instance, it has been shown that a lack of insulin signaling and GLUT4 movement completely explains the unhealthy glucose absorption in type 2 diabetes. The results add to these findings by showing that TRIO, ELMO2, and CSNK1G2 might be responsible for such deficiencies [10].

TRIO, ELMO2 and CSNK1G2 encode proteins that function in cytoskeletal reorganization, Rac1 signaling and vesicle transport — processes that are required for the action of insulin in stimulating GLUT4 translocation to the plasma membrane. TRIO and the cytoskeleton: TRIO is a Rho GTPase guanine nucleotide exchange factor for the regulation of the actin cytoskeleton. Dynamically, upon insulin signaling, rearrangements of the cytoskeleton occur that create the tracks and forces for vesicle transport of GLUT4. Downregulation of TRIO might gang up with this cytoskeletal remodeling to inhibit GLUT4 translocation [11].

ELMO2 acts on Rac1: ELMO2 works with Dock family members to activate a second Rho GTPase, Rac1. Membrane ruffling and actin polymerization, processes that support GLUT4 vesicle trafficking and GLUT4 fusion to the plasma membrane, are activities mediated by Rac1. Therefore, lowering ELMO2 would lower Rac1 activation which in turn lowers GLUT4 translocation [12,13].

CSNK1G2 and Protein Trafficking: CSNK1G2 is a serine/threonine kinase that participates in various cellular activities, including protein trafficking. Its direct involvement in GLUT4 trafficking has been much less characterized than that of TRIO and ELMO2, however, kinases have been known to influence vesicle budding, transport, and fusion. A downregulation of CSNK1G2 may disrupt normal trafficking of the GLUT4 vesicle [14].

Previous studies have also focused on the traditional insulin signaling pathway via PI3K/Akt. Our findings, however, show that the TRIO-ELMO2-CSNK1G2 pathway is an as-yet undervalued regulatory pathway in parallel or downstream to the traditional pathway to regulate GLUT4 translocation.

Previous work has mostly described the classical pathway of insulin signaling mainly in terms of PI3K activation and the role of downstream effector Akt in GLUT4 translocation [15]. This study, however, suggests that the TRIO-ELMO2-CSNK1G2 pathway is an underrated regulatory mechanism operating either parallel to or downstream of the classical pathway to regulate GLUT4 translocation and thus implies a more integrated and multi-faceted regulatory system [15-17].

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Conclusions

This paper reveals that the downregulated expression of TRIO, ELMO2, and CSNK1G2 might correlates with insulin resistance in muscle tissue, indicating that they could be involved in the pathogenesis of type 2 diabetes. All these genes encode proteins that play significant roles in cellular processes for GLUT4 translocation, and their downregulation likely underlies the disorder of glucose uptake characteristic of this metabolic disease. These findings suggest that suppression of these genes or the pathways to which they are associated may offer new therapeutic targets to increase insulin sensitivity and treat type 2 diabetes.

Limitations of the study:

There are a few limitations of this research. First, it is secondary analysis of publicly accessible data on gene expression. While this approach allows the comparison of changes in the expression of genes in human tissue, it relies on the quality and character of the original data set. The Pima Indian population's sample size and demographic characteristics, for instance, can influence how our finding generalizes to other populations. Second, our findings take into account only the expression levels of the genes. Further studies need to investigate protein expression and activity of TRIO, ELMO2, and CSNK1G2 in insulin-resistant tissue. Third, even though our data suggest that these genes may play a role in regulating GLUT4 translocation, functional experiments need to be performed to ascertain them directly as part of this process.

Future Directions:

Future research should strive to confirm these findings in more diverse, larger populations. Protein levels and TRIO, ELMO2, and CSNK1G2 phosphorylation in insulin-resistant tissues and cells would be further evidence of their roles in insulin resistance. In vitro and in vivo studies in cell lines and animal models would reveal the precise mechanisms by which these genes regulate GLUT4 trafficking and glucose uptake. Additionally, the therapeutic value of inhibiting TRIO, ELMO2, or CSNK1G2 for the treatment of type 2 diabetes should be explored.

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Conflicts of Interest: *The authors declares that there are no conflicts of interest.*

Abbreviations

GEO: Gene Expression Omnibus
NCBI: National Center for Biotechnology Information
GDS: GEO DataSets
TRIO: Trio Rho Guanine Nucleotide Exchange Factor
ELMO2: Engulfment And Cell Motility 2
CSNK1G2: Casein Kinase 1 Gamma 2
GLUT4: Glucose Transporter Type 4
Rac1: Ras-related C3 botulinum toxin substrate 1

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