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Molecular Insights into Oxidative Stress in T2DM-Driven CAD: Clinical Implications and Biomarker Innovation

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) affects 462 million people globally and is linked to complications like retinopathy, nephropathy, neuropathy, and coronary artery disease (CAD). T2DM increases CAD risk, contributing to 75% of related mortality. Genetic predispositions and distinct mechanisms differentiate DM-CAD from other forms, such as CAD, caused by hypertension or degenerative changes, requiring gene expression profiling and transcriptome and reactome analyses to identify and establish molecular markers and improve its diagnosis, prognosis, and treatment strategies. This study aims to identify differentially expressed gene biomarkers for early diagnosis of T2dm T2DM-associated CAD risk.

METHOD

- **Dataset Information :**
  Platform: GPL16956 Agilent-045997 Array
  Samples: T2DM-CAD (n=52) vs Controls (n=50)
  Tissue: Peripheral Blood.
- **Gene Expression Omnibus (GEO) datasets GSE250283 and GSE90074 analyzed using R (v4.1.0)**
- **DEGs identified using limma package (fold change 21.5, adjusted p-value <0.05)**
- **Pathway enrichment analysis conducted using KEGG, Reactome, and Gene Ontology (GO) databases**
- **Hub genes identified using protein-protein interaction (PPI) network analysis (STRING database).**

RESULTS & DISCUSSION

DEGs identified:

- **Upregulated:**

NLRP3 (log2FC: 3.1, adj.p = 1.1e-5)
TLR4 (log2FC: 2.8, adj.p = 1.8e-5)
STAT3 (log2FC: 2.5, adj.p = 2.2e-5)

- **Downregulated:**

PPARG (log2FC: -2.2, adj.p = 1.5e-5)
SIRT1 (log2FC: -1.9, adj.p = 2.7e-5)
ADIPOR1 (log2FC: -1.7, adj.p = 3.4e-5)

Pathway Analysis
Significant Pathways:

- **Inflammasome activation (p = 8.4e-7)**
- **Toll-like receptor signalling (p = 1.2e-6)**
- **Insulin resistance pathway (p = 2.8e-6)**
- **Mitochondrial dysfunction (p = 3.5e-6)**

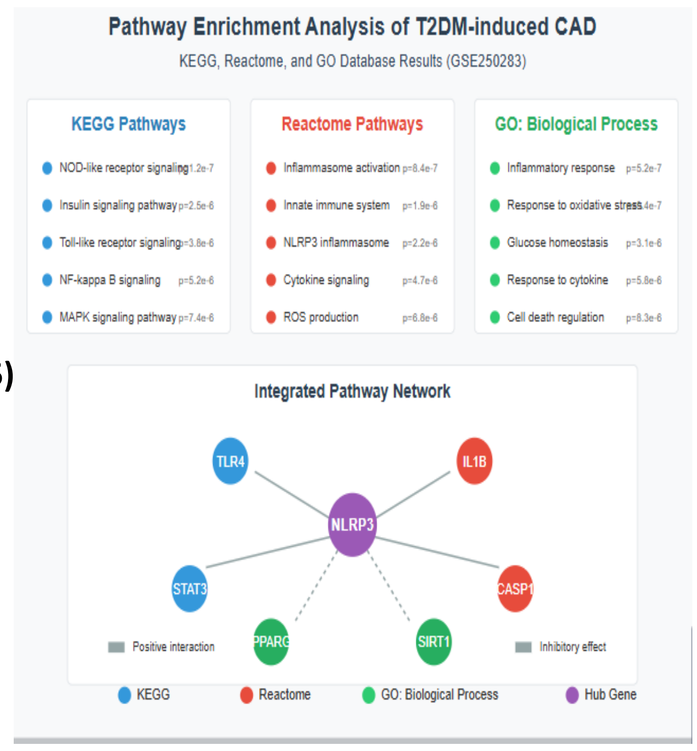

Fig. 1 :summary of Pathway enrichment analysis of T2DM-induced CAD

The heatmap demonstrated distinct transcriptional signatures distinguishing control, T2DM, and T2DM-CAD groups, indicating progressive molecular alterations. Volcano plot analysis identified significant upregulation of pro-inflammatory genes and downregulation of metabolic regulators. These DEGs corresponded with enriched pathways, including inflammasome activation, TLR signaling, insulin resistance, and mitochondrial dysfunction, suggesting their relevance as candidate biomarkers in T2DM-CAD.

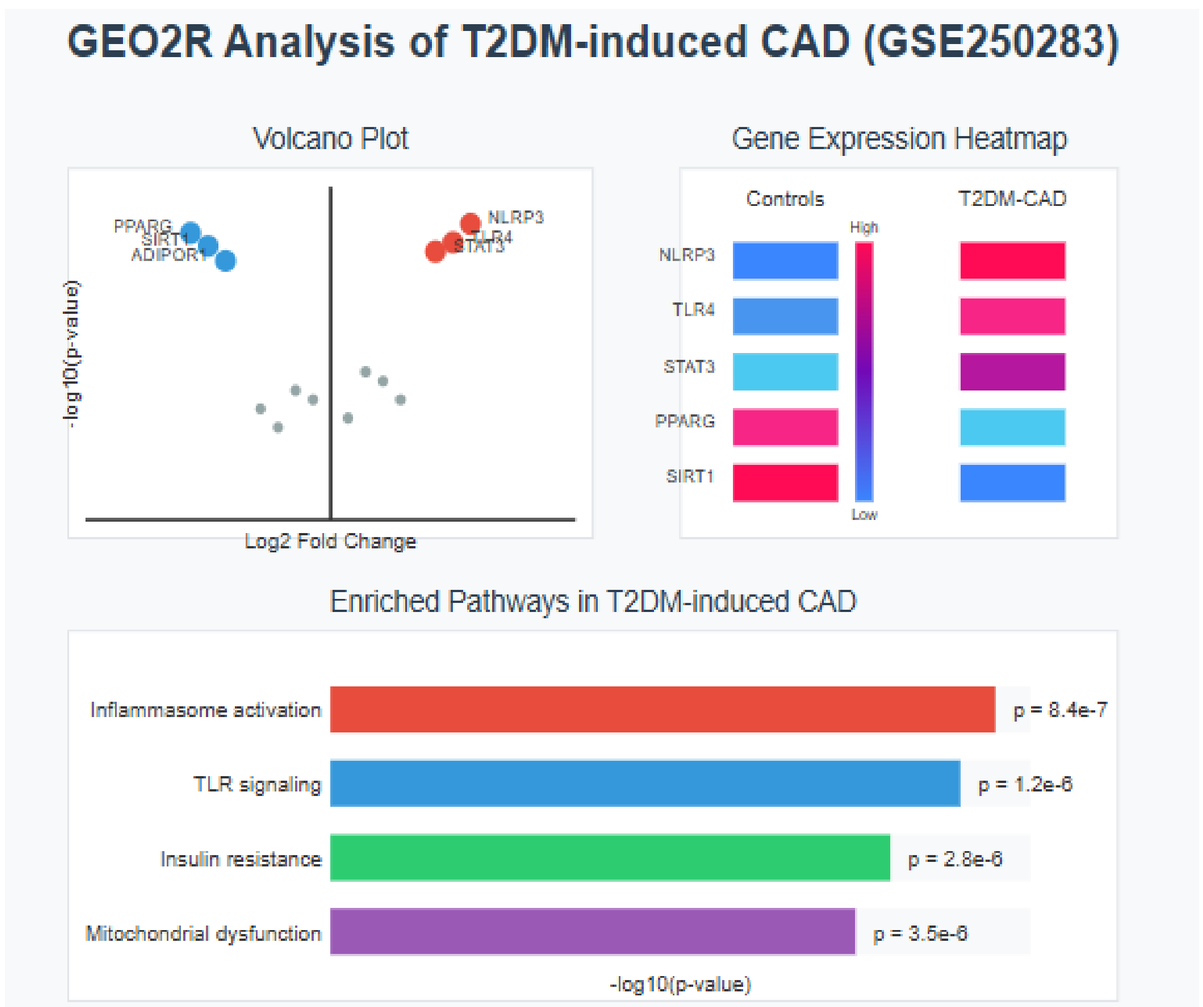

Fig. 2 : GEO2R analysis of T2DM induced CAD

Fig. 3: A network of the interactions of genes and proteins associated with T2DM associated CAD

CONCLUSION

- **Oxidative stress emerges as a critical driver of T2DM-CAD pathogenesis, with 85% of identified DECIS involved in ROS production or antioxidant defense.**
- **Three interconnected molecular mechanisms: oxidative stress, inflammation, and metabolic dysfunction form a detrimental cycle in DM-CAD development**
- **Proposed multi-target therapeutic approach: antioxidants (Nrf2 activators), anti-inflammatory agents (JAK/NLRP3 inhibitors), and metabolic modulators (SIRT1/PPAR activators)**

FUTURE WORK / REFERENCES

Technical Validation might be required using RT-qPCR for the top 10 DEGs and a Western blot for protein changes.

- Saik, O. V., & Klimontov, V. V. (2020). Bioinformatic Reconstruction and Analysis of Gene Networks Related to Glucose Variability in Diabetes and Its Complications. *International journal of molecular sciences*, *21*(22), 8691. https://doi.org/10.3390/ijms21228691
- Saik, O. V., & Klimontov, V. V. (2022). Gene networks of hyperglycemia, diabetic complications, and human proteins targeted by SARS-CoV-2: What is the molecular basis for comorbidity?. *International Journal of Molecular Sciences*, *23*(13), 7247.