Uncovering the genes linking glucose variability with endothelial dysfunction in diabetes by the analysis of gene networks

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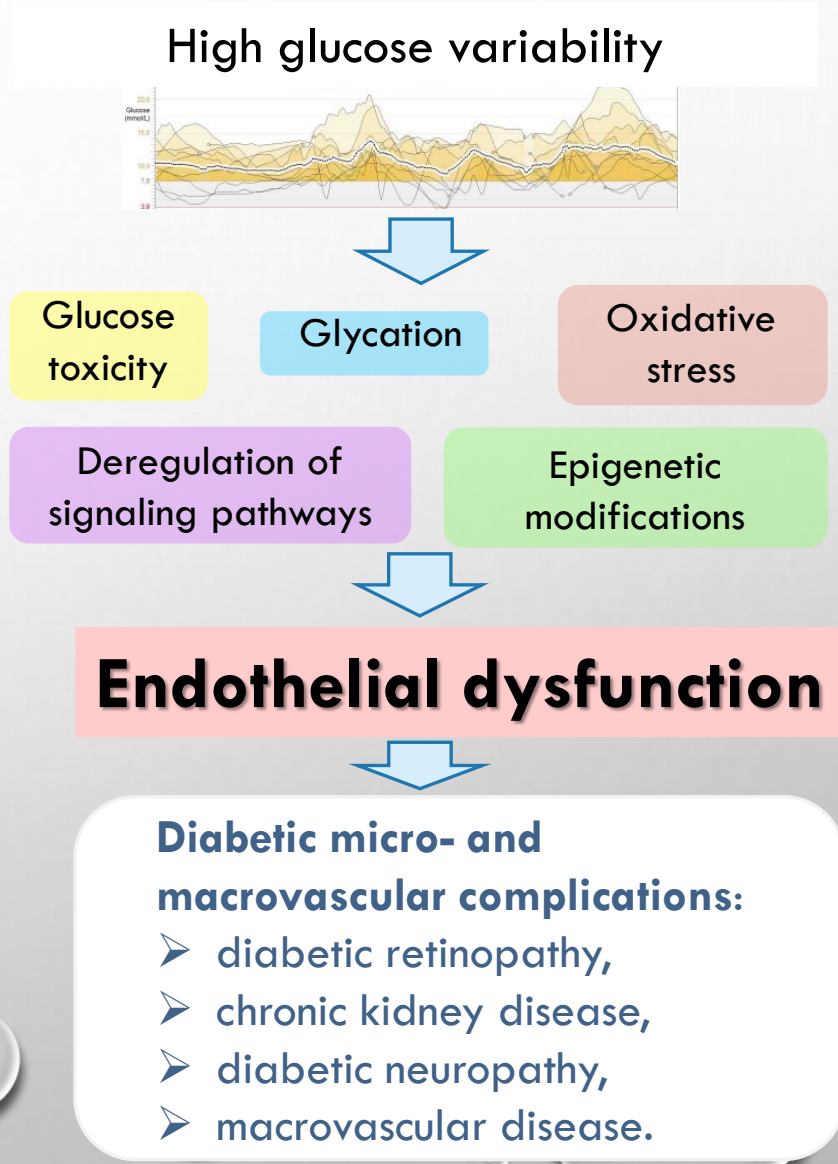
Motivation and aim

- High glucose variability (GV) is recognized as a contributor for diabetic microvascular and macrovascular complications, including diabetic retinopathy, chronic kidney disease, diabetic neuropathy, and macrovascular disease.
- The results of numerous studies have pointed to the role of endothelial dysfunction in the development of these complications.

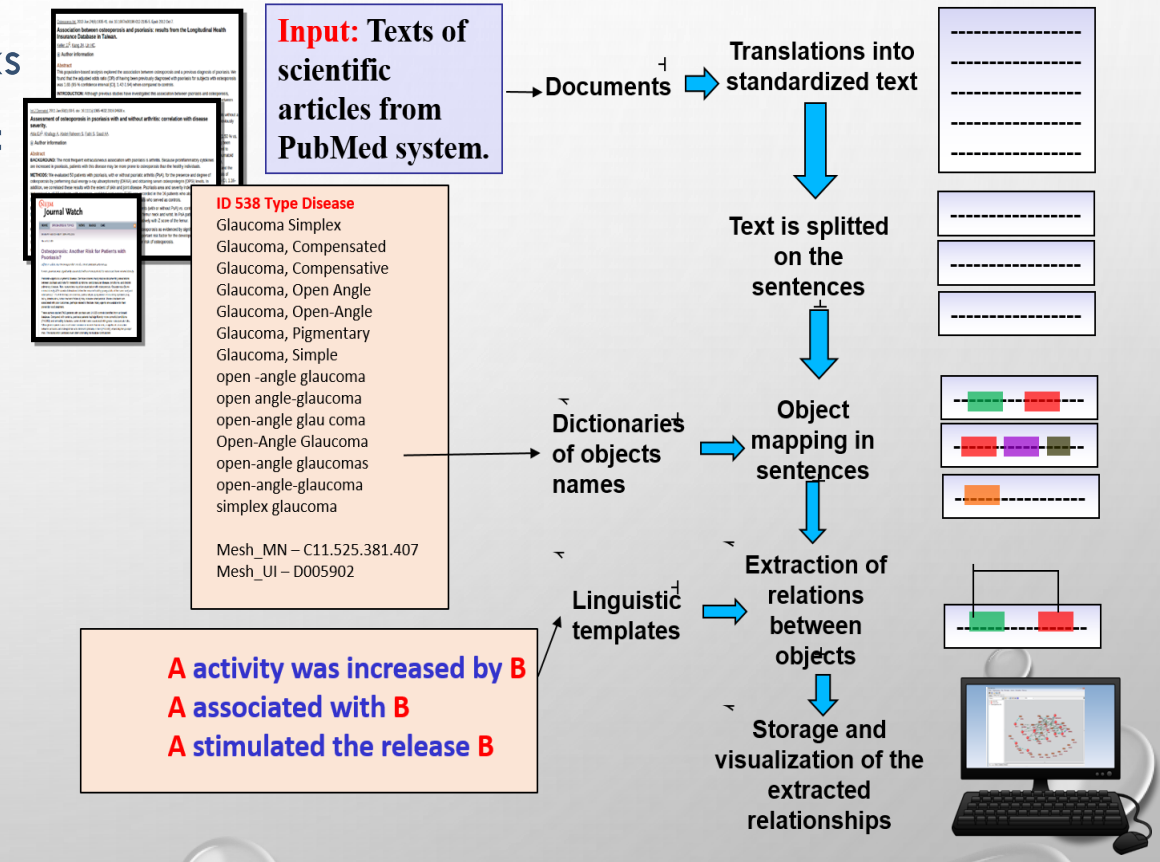


The aim: to identify genes linking GV with endothelial dysfunction in diabetes.

Methods

- The gene networks reconstruction and analysis were performed by the ANDSystem (www-bionet.sscc.ru/and/cell/).
- The statistical significance of the enrichment of gene networks by common genes was assessed according to hypergeometric distribution calculated by the "hypergeom.sf" function of Python "scipy.stats" module.
- The analysis of biological processes overrepresentation for the list of common genes was performed by the web-service DAVID (david.ncifcrf.gov/).
- The values of betweenness centrality were calculated by the "Analysis" function of ANDSystem.
- The Mann-Whitney U test was performed by the "mannwhitneyu" function of Python "scipy.stats" module.

Scheme of ANDSystem

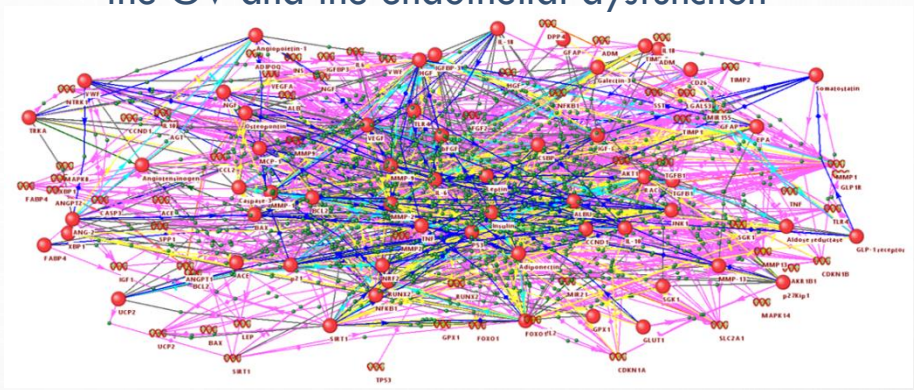


Results

Based on the information from ANDSystem the gene networks of the GV and the endothelial dysfunction were reconstructed. These gene networks contained 151 and 682 genes/proteins respectively.

Intersection of two networks (60 genes/proteins)

60 genes/proteins that are common for both the GV and the endothelial dysfunction



- According to hypergeometric distribution the probability of observing 60 common genes for random reasons is very small (p-value<10^{-47}).
- The identified 60 common genes/proteins are involved in the activation, apoptosis, development, differentiation, migration, morphogenesis and proliferation of endothelial cells according to the results of the Gene Ontology enrichment analysis.
- It was found that in the GV gene network many genes associated with endothelial dysfunction have relatively high values of betweenness centrality. The average of betweenness centrality values for the common 60 genes involved in endothelial dysfunction and GV was 536, while for all GV genes it was only 270. The difference of the betweenness centrality values for these two gene sets is statistically significant (P-value=10^{-5}, Mann-Whitney U test).
- All the top ten genes with highest betweenness centrality values in the GV gene network (*INS, IL6, TP53, FOXO1, LEP, MAPK14, TNF, IL1B, IGF1,* and *VEGFA*) were also involved in the endothelial dysfunction.

Conclusion

Discovering the key genes involved both in the GV and endothelial dysfunction could shed light on understanding of the pathogenesis of diabetes complications and could support the future drug development.

Thank you for your attention!

ACKNOWLEDGMENT

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