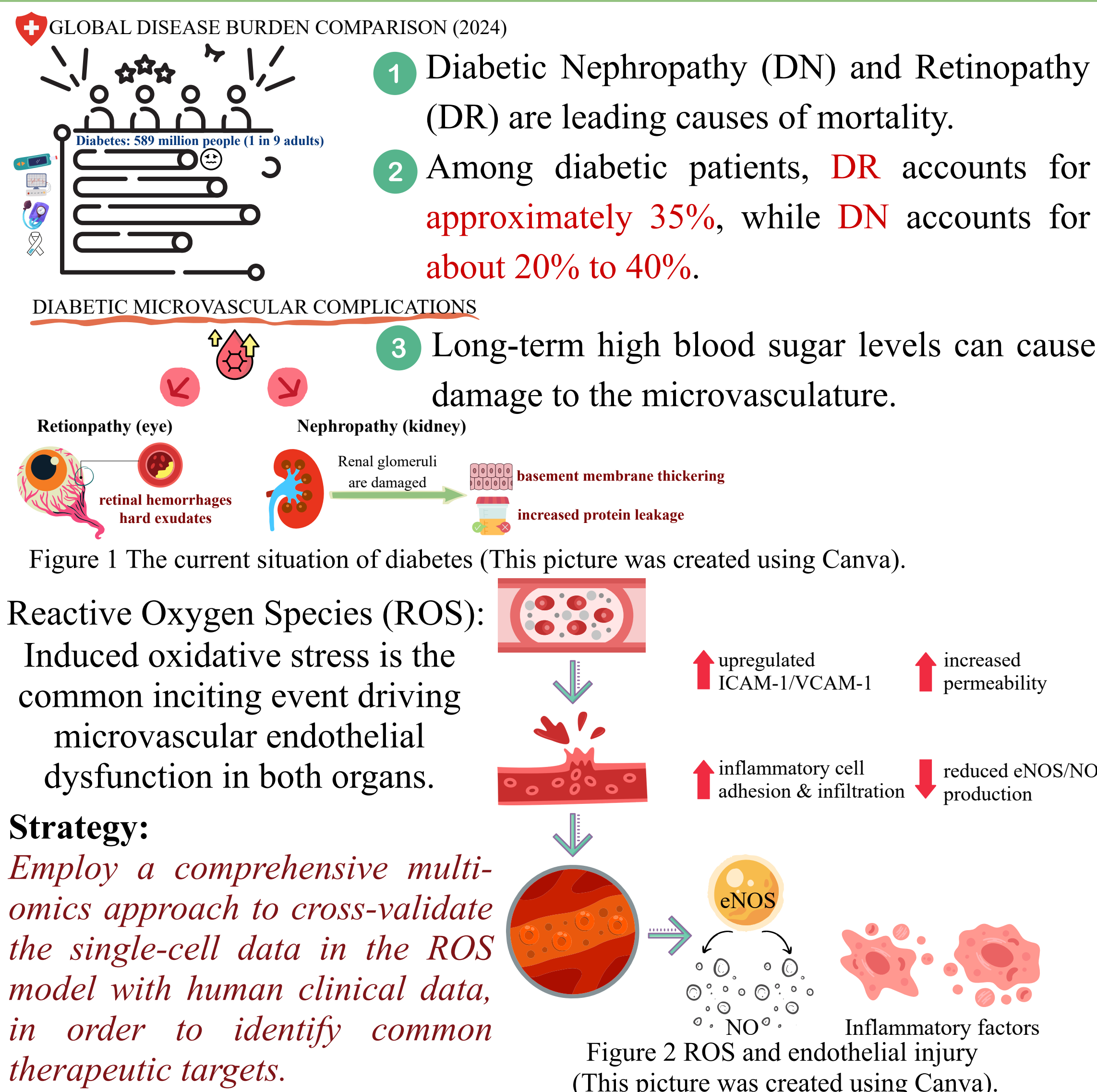
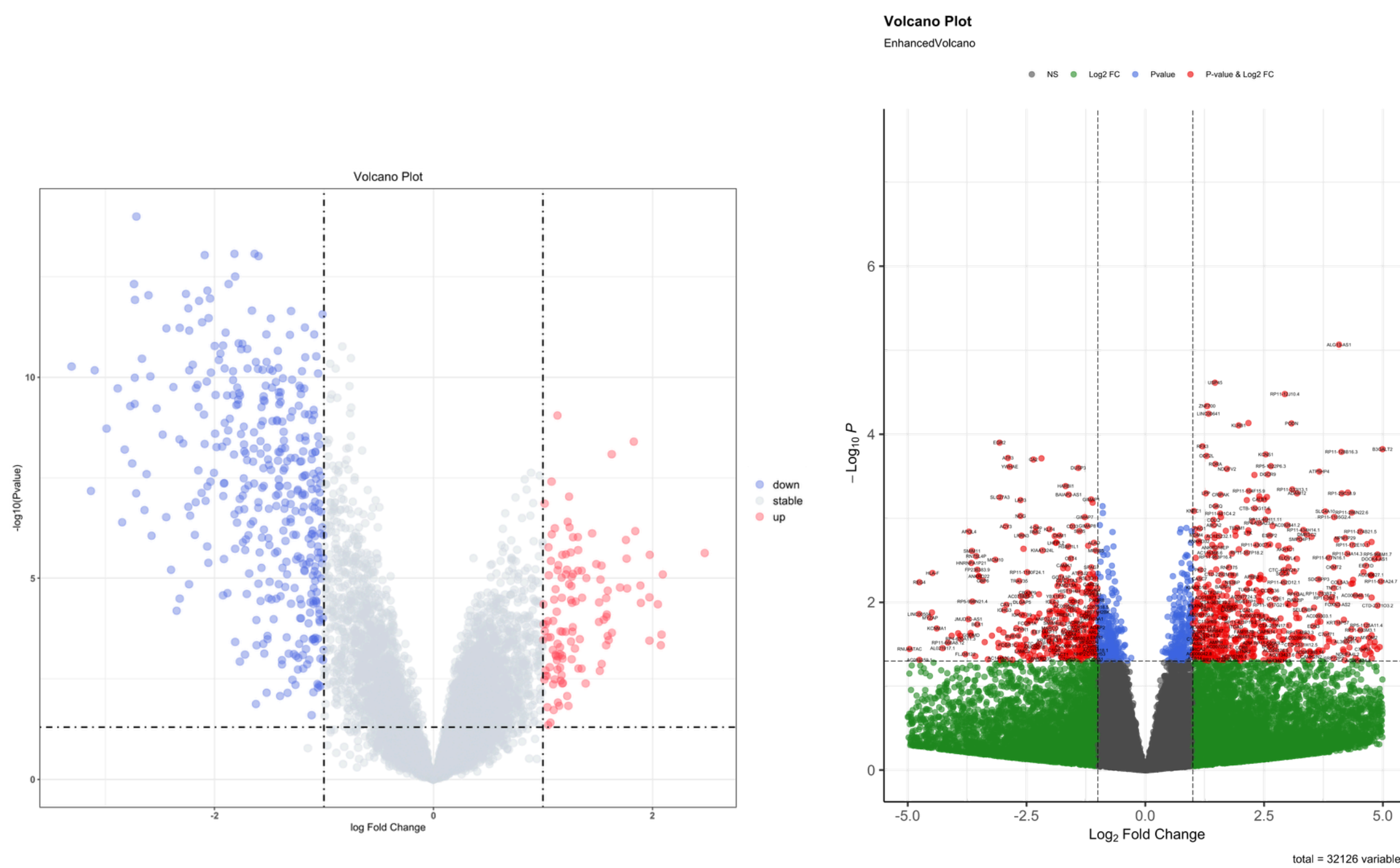


Identification of Candidate Biomarkers for Diabetic Complications via High Glucose-Induced Endothelial Injury Mechanisms

Introduction & Motivation



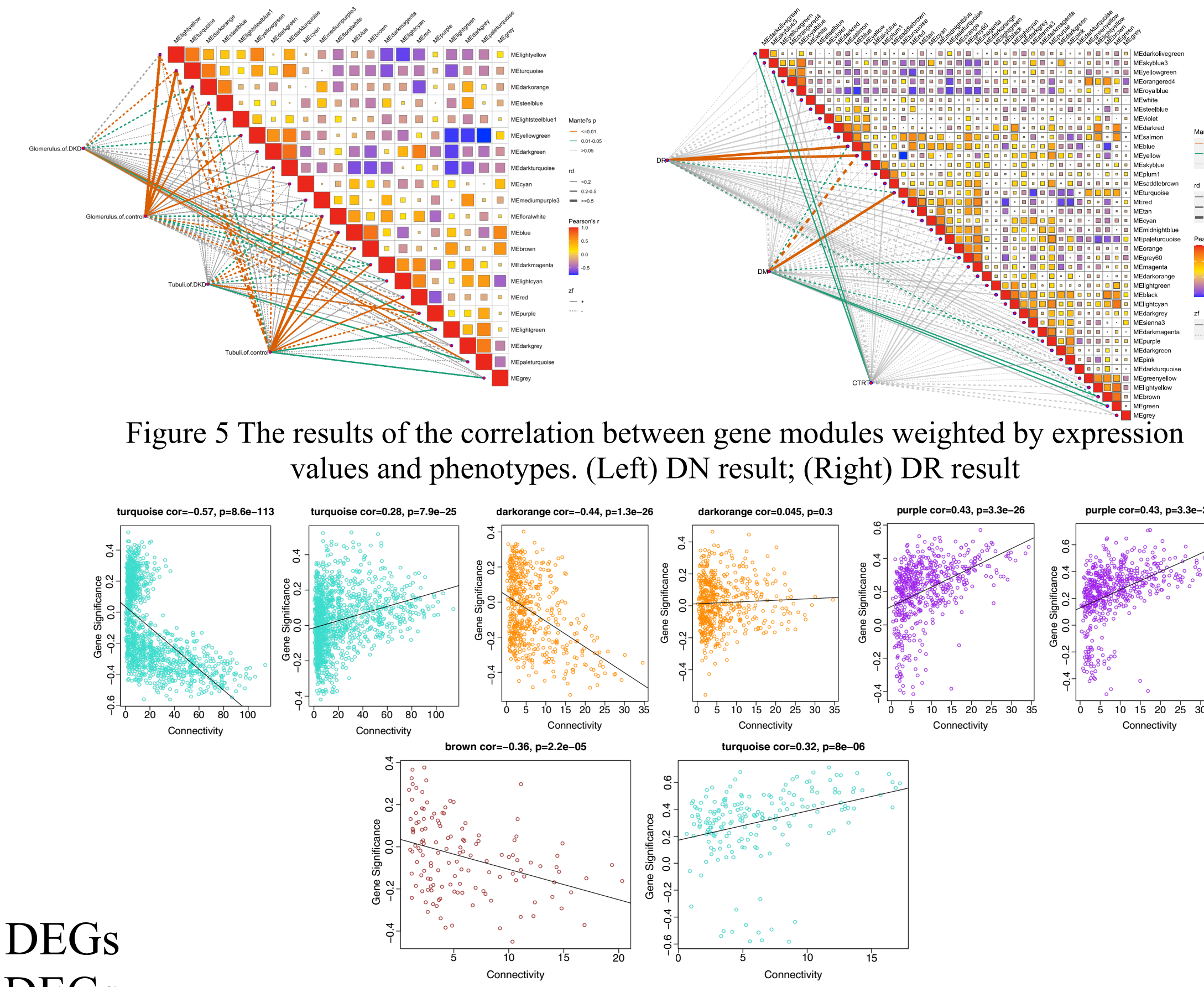
1. Differentially expressed genes in the DN and DR groups



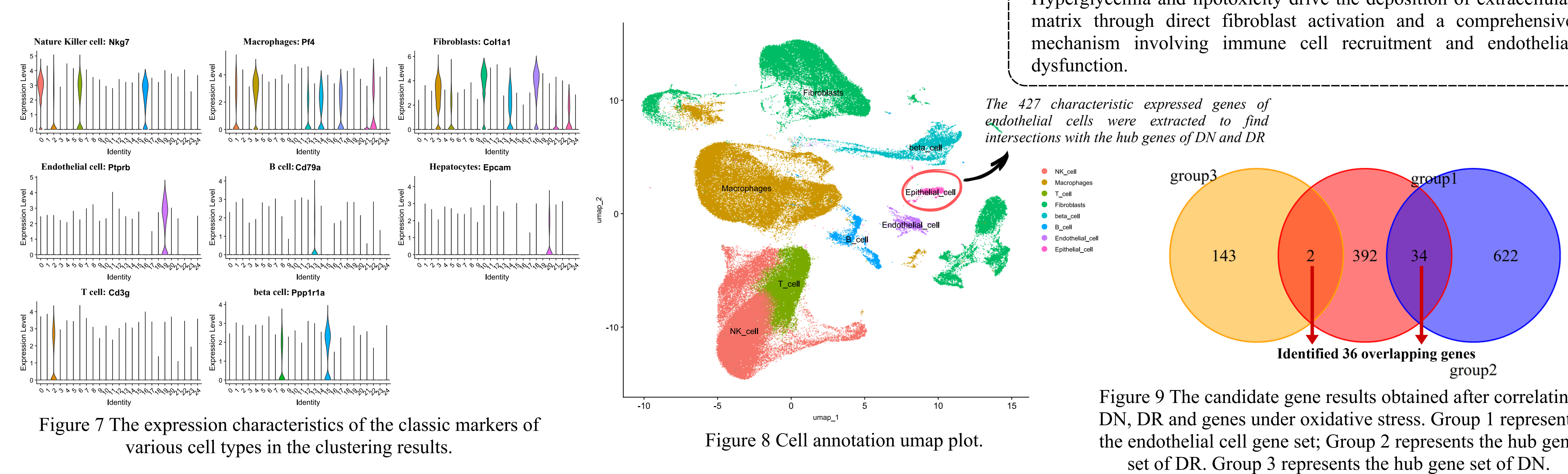
DEGs were selected based on the condition that $|\log_2FC| > 1$ & $P\text{value} < 0.05$

DN: A total of 505 DEGs
DR: A total of 969 DEGs

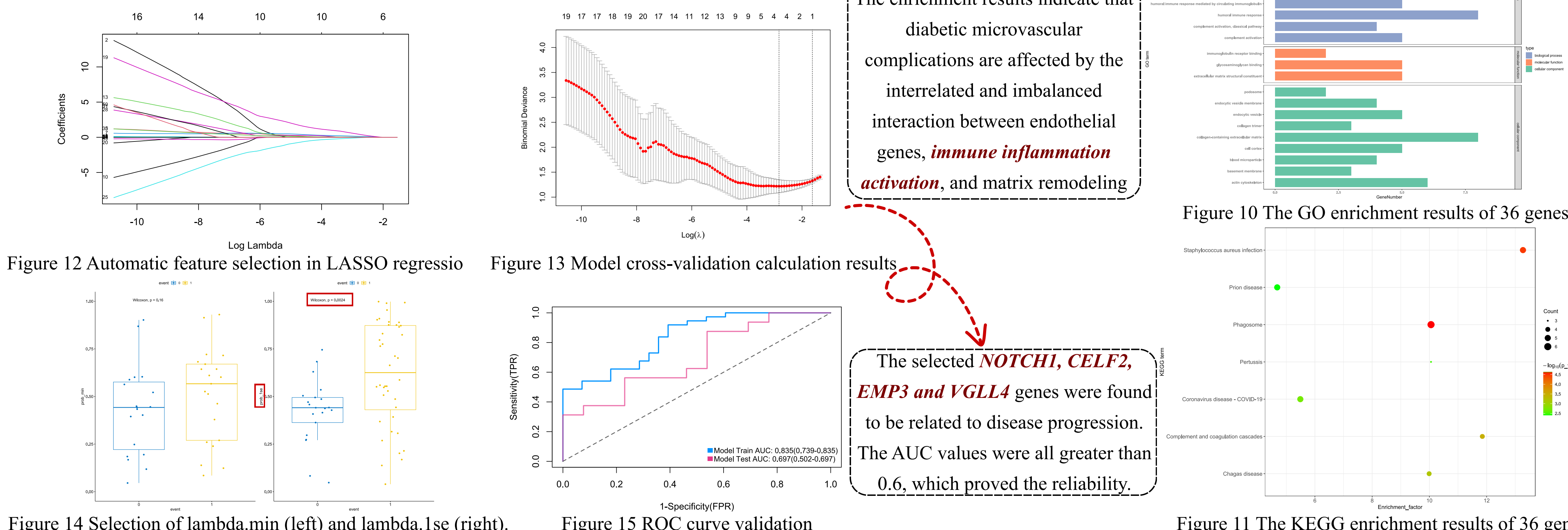
2. Genetic modules that are significantly associated with phenotypic expression



3. Determine the genes related to diseases based on the single-cell results of the combined oxidative stress state



4. Selection of candidate biomarkers associated with disease progression based on LASSO regression

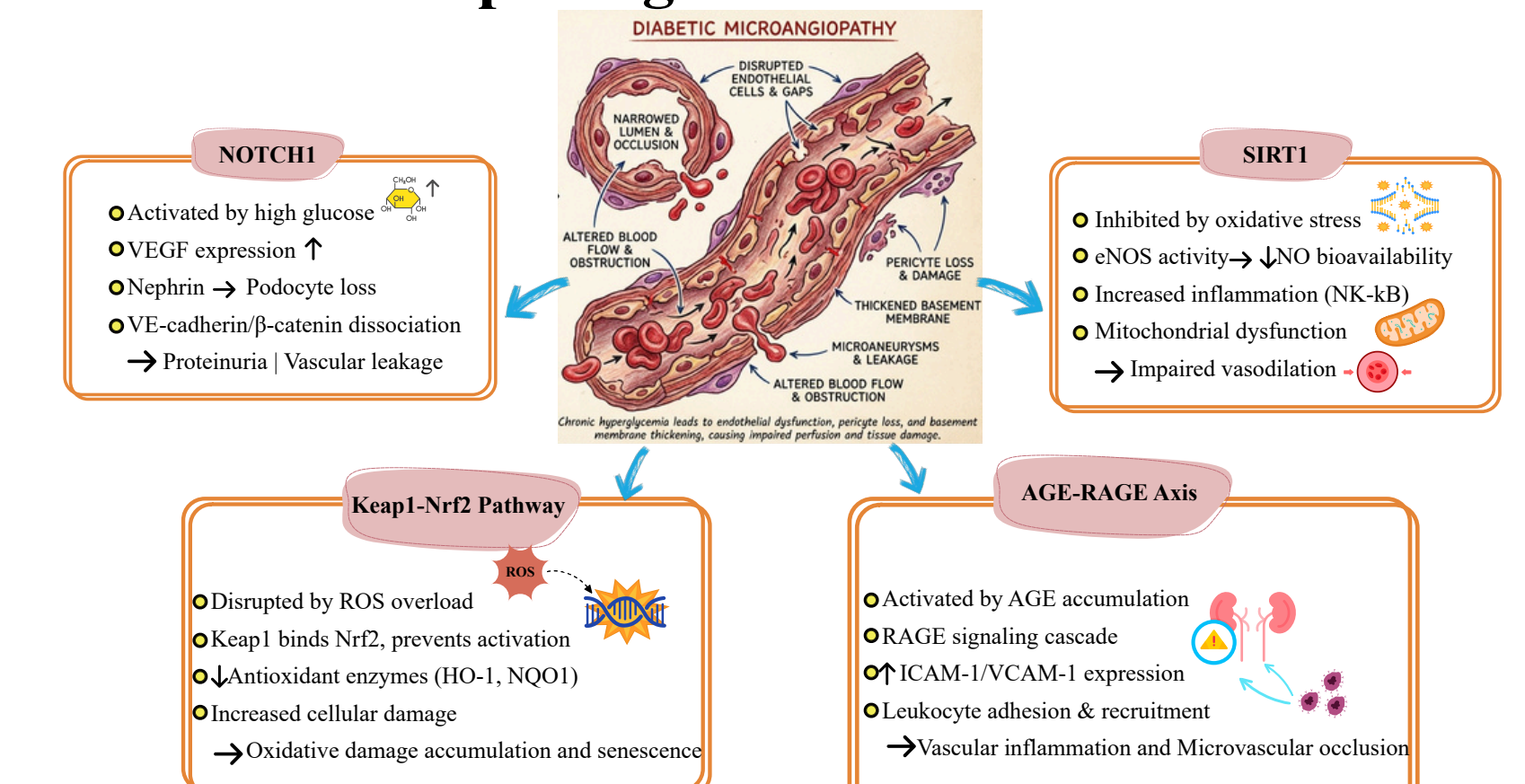


Discussion

The common characteristics exhibited by DN and DR are manifested as thickening of the microvascular basement membrane, absence of pericytes, and extensive endothelial dysfunction. Therefore, the results of this study provide a new mechanism-based explanation:

Endothelial cells are the direct targets of high glucose-induced damage, and endothelial cell dysfunction can mediate mesenchymal transformation to promote fibrotic remodeling.

- Under high sugar conditions, the **NOTCH1** signal is significantly activated, leading to the loss of podocytes and the disruption of tight junctions.
- Significant dysregulation of **CEL2** may disrupt the splicing mechanism of endothelial cells, leading to a "splicing stress" state and the loss of the ability to eliminate ROS.
- **EMP3** can mediate the endothelial-mesenchymal transition process and drive the transformation of a pro-fibrotic phenotype (indicating tissue damage).
- **VGLL4** is involved in the homeostasis of endothelial cells, and its dysfunction can lead to pathogenic neovascularization.



Future Application

NOTCH1, **CEL2**, **EMP3** and **VGLL4** each demonstrate direct or indirect involvement in diabetic vascular damage at different levels, providing new research targets for subsequent functional verification and future drug development.

Future research plan:

Short-term (cell experiments): Focus on verifying the effects using the splicing target of **CEL2** and the endothelial-mesenchymal transition induced by **EMP3**.

Medium-term (animal models): Develop endothelial cell-specific knockout mice to verify the protective effect in diabetes models.

Long-term (clinical): Develop diagnostic reagents for analysis of clinical samples.

Selected References

- Al-Lawati, J. A. (2020). Diabetes mellitus: A public health challenge. *World Journal of Diabetes*, 11(12), 478–494. <https://doi.org/10.4239/wjcd.v11.i12.478>
- An, Y., Xu, B.-T., Wan, S.-R., Ma, X.-M., Long, Y., Xu, Y., & Jiang, Z.-Z. (2023). The role of oxidative stress in diabetes mellitus-induced vascular endothelial dysfunction. *Cardiovascular Diabetology*, 22(1), 237. <https://doi.org/10.1186/s12933-023-01965-7>
- Chen, W., Wang, J., Lin, H., Wu, C., Liang, H., & Li, G. (2023). A single-cell transcriptomic atlas of the diabetic mouse retina reveals the early cellular response to hyperglycemia. *Cell Reports*, 42(6), 112554. <https://doi.org/10.1016/j.celrep.2023.112554>

Research Hypothesis

It has been ascertained:

- DN and DR both represent microvascular lesion outcomes in different tissues. —**Focus on the entire category**
- Oxidative stress is one of the main changes that lead to endothelial dysfunction

Hypothesis:

By characterizing the key regulatory genes in the reactive oxygen network, potential biomarkers that can exert intervention and therapeutic effects on both DN and DR will be discovered.

Methods

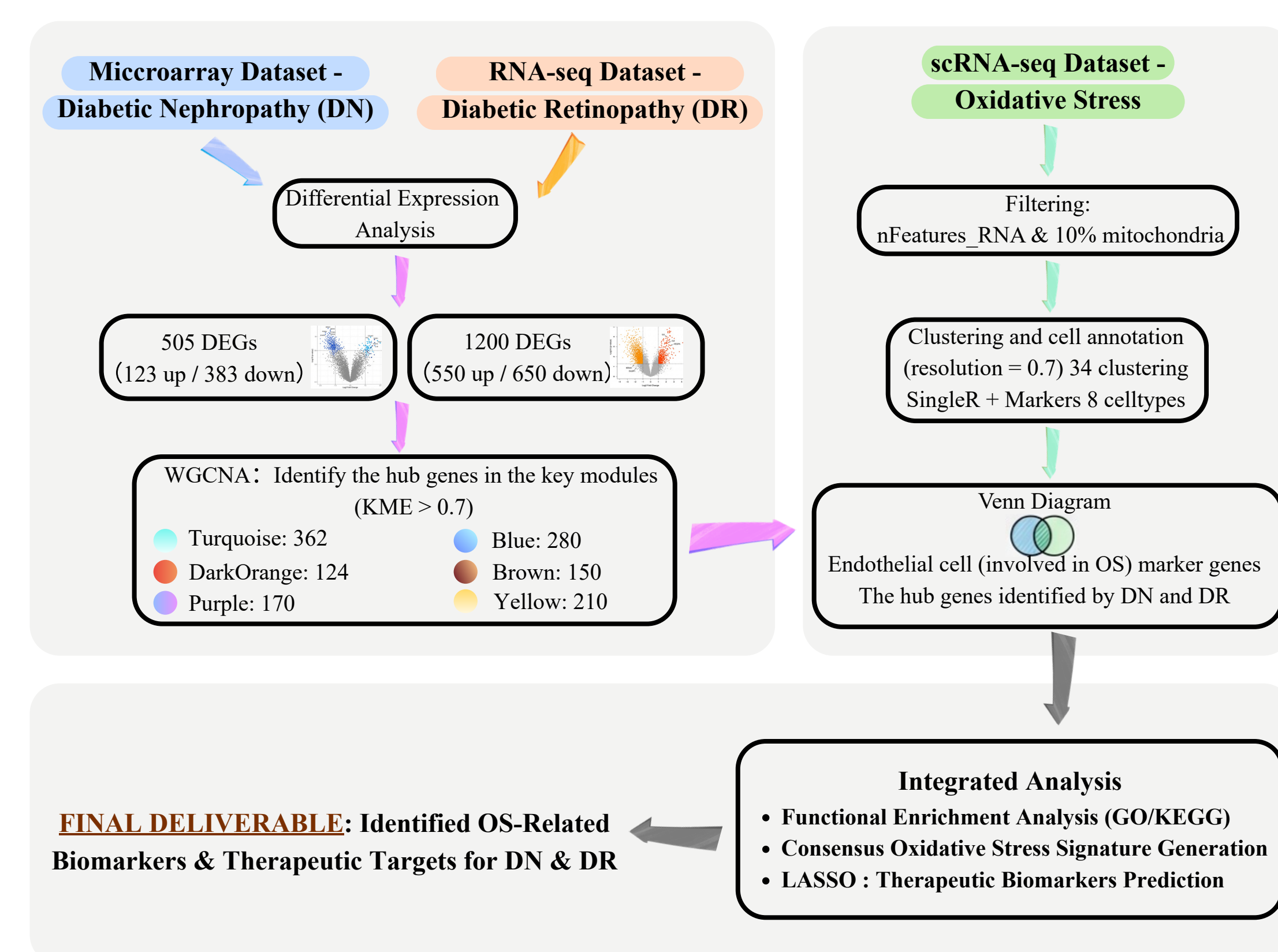


Figure 3 The process design for data analysis presentation (The flowchart above was created using Canva).