Table 1. Donor Characteristics

	Non-Diabetic (N=5)	Diabetic (N=5)	Total (N=10)
Sex			
- Male	3 (60%)	4 (80%)	7 (70%)
- Female	2 (40%)	1 (20%)	3 (30%)
Age (yrs)			
- Mean (SD)	38.6 (12.2)	50.4 (8.4)	44.5 (11.7)
- Min - Max	22.0 - 54.0	42.0 - 61.0	22.0 - 61.0
Race/Ethnicity			
- White	3 (60%)	1 (20%)	4 (40%)
- Black or African American	2 (40%)	0 (0%)	2 (20%)
- Hispanic or Latino	0 (0%)	3 (60%)	3 (30%)
- Asian	0 (0%)	1 (20%)	1 (10%)
BMI			
- Mean (SD)	33.0 (11.7)	35.3 (10.1)	34.1 (10.4)
- Min - Max	16.0 - 46.2	24.0 - 48.4	16.0 - 48.4
BMI Classification			
- Underweight	1 (20%)	0 (0%)	1 (10%)
- Healthy Weight	0 (0%)	1 (20%)	1 (10%)
- Overweight	1 (20%)	1 (20%)	2 (20%)
- Obese	3 (60%)	3 (60%)	6 (60%)
Mechanism of Death			
- Stroke	2 (40%)	4 (80%)	6 (60%)
- Cardiovascular - Anoxia	2 (40%)	0 (0%)	2 (20%)
- Head trauma - Blunt Injury	1 (20%)	0 (0%)	1 (10%)
- Head trauma - Gunshot	0 (0%)	1 (20%)	1 (10%)

Transcriptomics

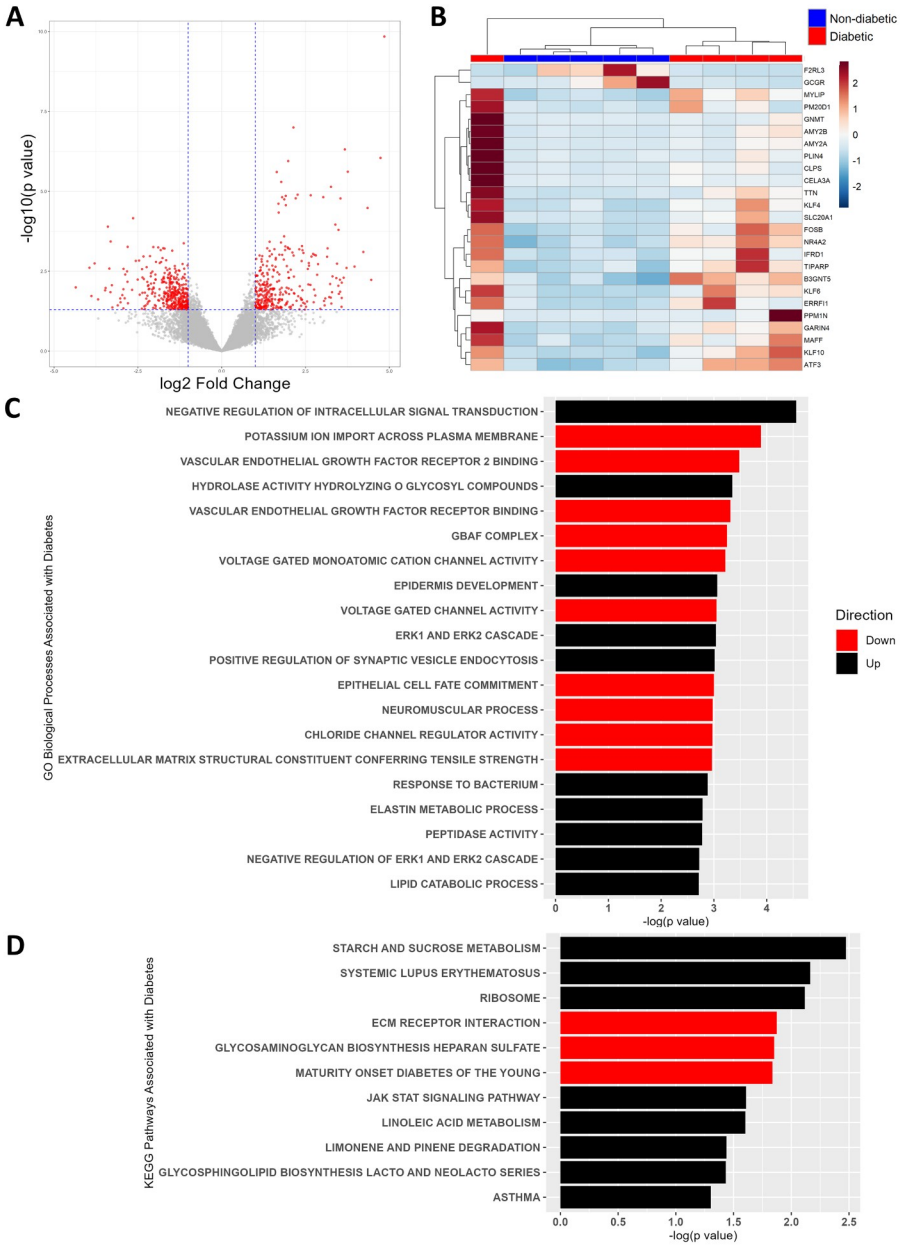

Figure 1. Transcriptomic differences in islet cells from diabetic vs non-diabetic donors
A) Volcano plot visualizing differential gene expression results. The x-axis represents fold-change (log2) in islet cells from diabetic vs. non-diabetic donors, delineating up-regulated (right) and down-regulated (left) genes. The y-axis shows -$\log_{10}$(adjusted p-value). Red points represent genes with fold change >|2| and p<0.05. Top differentially expressed genes are labeled. **B)** Heatmap representation of relative levels of transcripts differentially abundant (FDR p-adjusted<0.1) in diabetic and non-diabetic islet cells by Wald test. Clustering by Ward's algorithm, expression values scaled by row. **C)** The top 10 up- and 10 down-regulated Gene Ontology (GO) Biological Processes and **D)** Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathways enriched in genes differentially expressed between diabetic and non-diabetic islet cells (p<0.05), derived from Gene Set Enrichment Analysis (GSEA) against gene sets in the Human Molecular Signatures Database (HMSD). Genes were ranked by the product of their $\log_2$(fold change) in expression between diabetic and non-diabetic islets and their $\log_{10}$(p value) derived from DESeq2 analysis. Red bars indicate Processes/Pathways with enrichment scores (ES) less than zero, indicating their enrichment in genes with lower expression in diabetic samples and suggesting their down-regulation, whereas those with ES greater than zero are depicted in black, suggesting up-regulation.

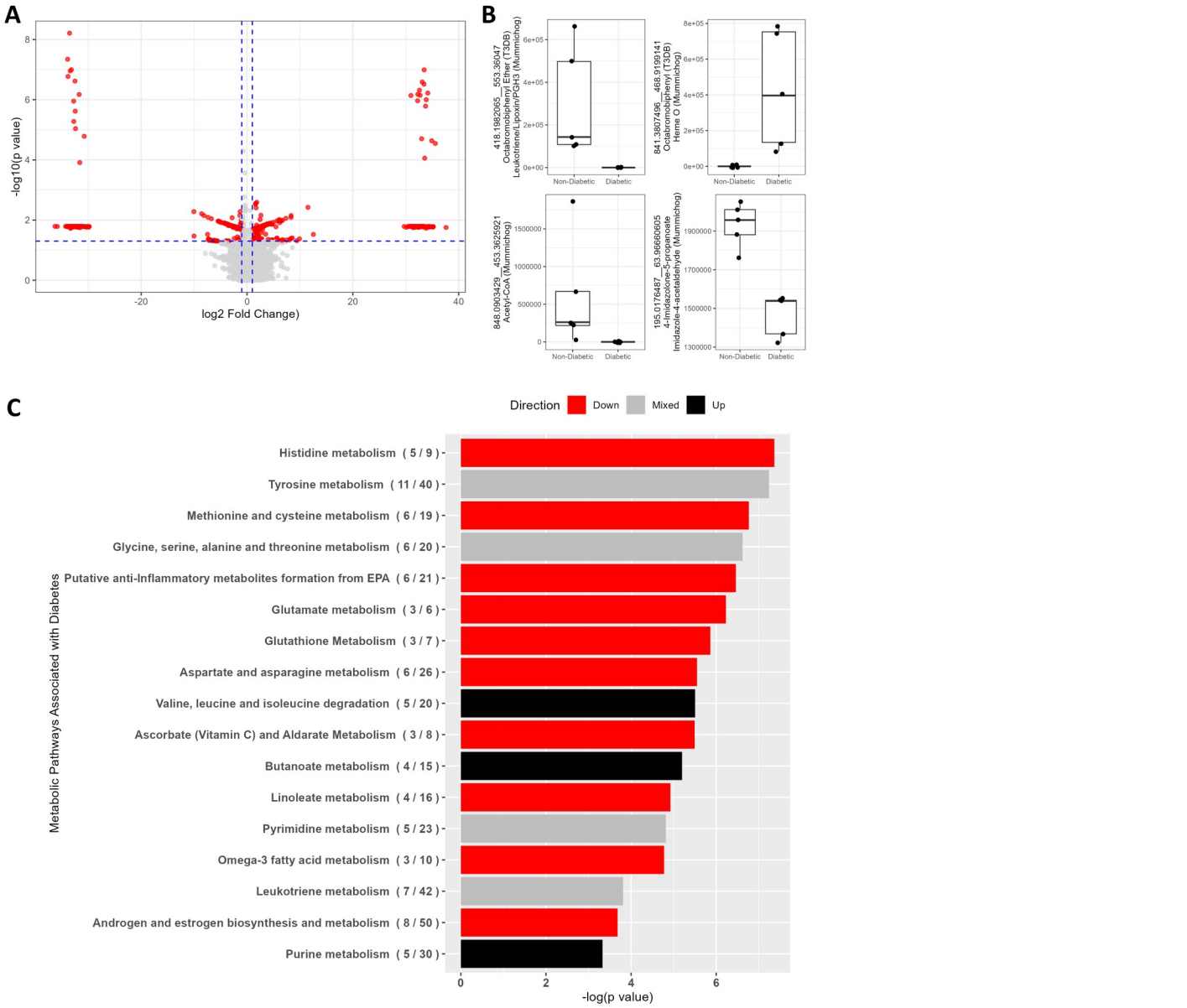

Figure 2. Metabolomic differences in islet cells from diabetic vs non-diabetic donors

A) Volcano plot visualizing differential metabolomic feature intensity. The x-axis represents fold-change (log2) in normalized metabolomic feature intensity in islet cells from diabetic vs. non-diabetic donors, delineating features more (right) or less (left) abundant in samples from diabetic donors. The y-axis shows $-\log_{10}$(p value) derived from t tests. Red points represent features with raw p<0.05 and fold change >|2|. **B)** Raw and normalized intensity values of annotated metabolomic features differentially abundant in diabetic and non-diabetic islet cells at FDR-adjusted p<0.1 by t tests. Features are identified by mass:charge ratio (mz) and retention time (rt; mz_rt) and by annotations derived from the Toxin and Toxin Target Database (T3DB) matches and mummichog assignments. **C)** Metabolic pathways enriched in metabolites differentially abundant (t test p<0.05) between diabetic and non-diabetic islet cells. Pathway p values assigned by mummichog algorithm take into account the number of differentially abundant features assigned to a pathway relative to the total number of features in the data set assigned to that pathway [(# differentially abundant features / # total features)]. Only pathways with p<0.05 and at least three features assigned to them which were differentially abundant between the two groups were considered. Red bars indicate that pathways were enriched in putative metabolites less abundant in diabetic islets compared to non-diabetic. Black bars indicate that pathways were enriched in putative metabolites more abundant in diabetic islets. Gray bars indicate that a mixture of putative metabolites more and less abundant in diabetic islets were assigned to that pathway.

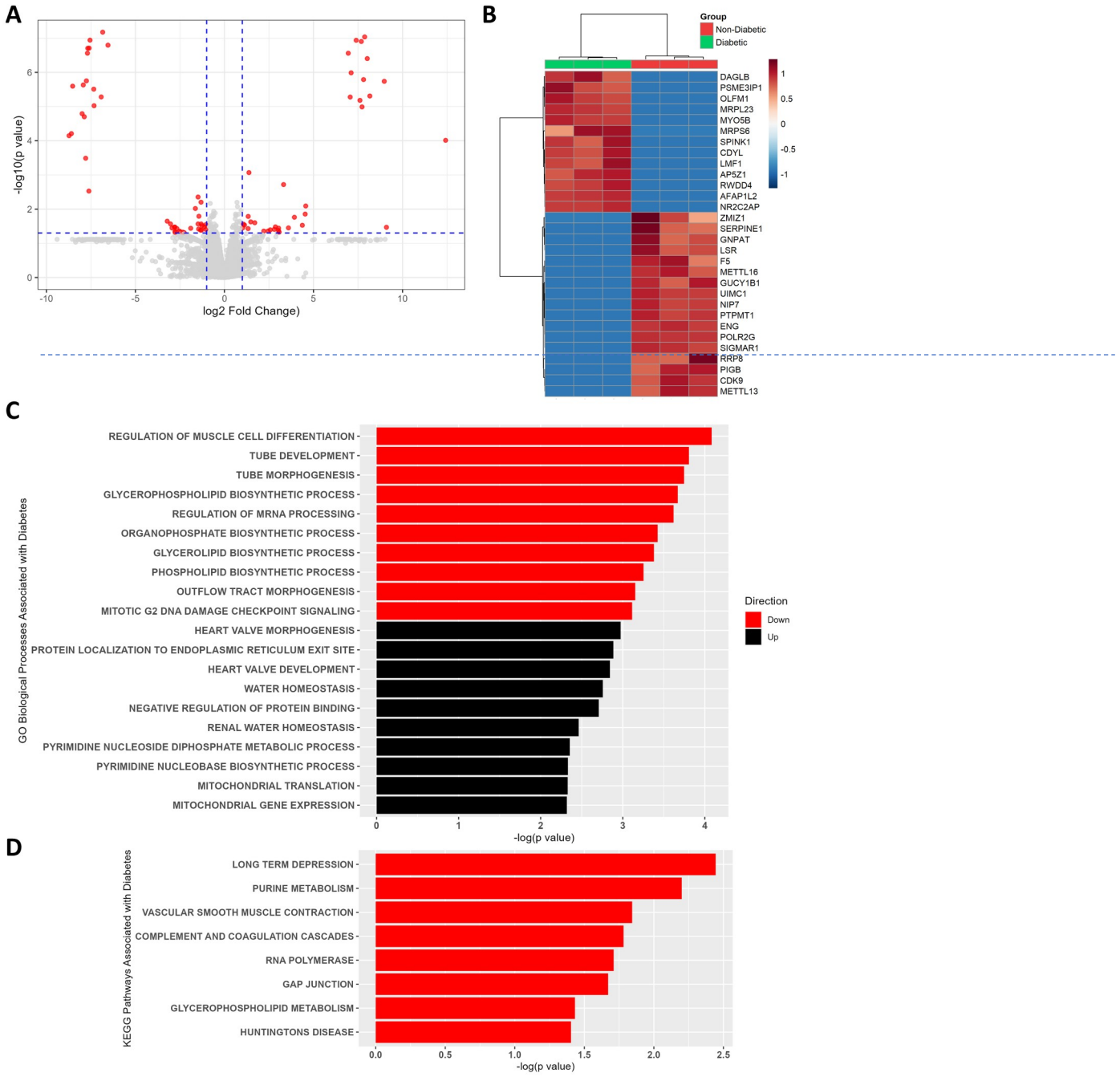

Figure 3. Proteomic differences in islet cells from diabetic vs non-diabetic donors

A) Volcano plot visualizing differential abundance of proteins. The x-axis represents fold-change (log2) in $\log_{10}$-transformed protein H/L ratios in islet cells from diabetic vs. non-diabetic donors, delineating features more (right) or less (left) abundant in samples from diabetic donors. The y-axis shows $-\log_{10}$(p value) derived from limma. Red points represent features with raw $p<0.05$ and fold change $>|2|$. **B)** Heatmap representation of relative levels of proteins differentially abundant (FDR p-adjusted<0.1) in diabetic and non-diabetic islet cells by limma. Proteins are identified by gene symbol for legibility. Clustering by Ward's algorithm, log-transformed protein H/L ratios scaled by row. **C)** The top 10 up- and 10 down-regulated GO Biological Processes and **D)** KEGG Pathways enriched in proteins differentially expressed between diabetic and non-diabetic islet cells ($p<0.05$), derived from GSEA against gene sets in the HMSD. Proteins were ranked by the product of their $\log_2$(fold change) in normalized H/L ratios between diabetic and non-diabetic islets and their $\log_{10}$(p value) derived from limma analysis. Red bars indicate Processes/Pathways with ES less than zero, indicating their enrichment in proteins with lower expression in diabetic islet samples and suggesting their down-regulation, whereas those with ES greater than zero are depicted in black, suggesting up-regulation.

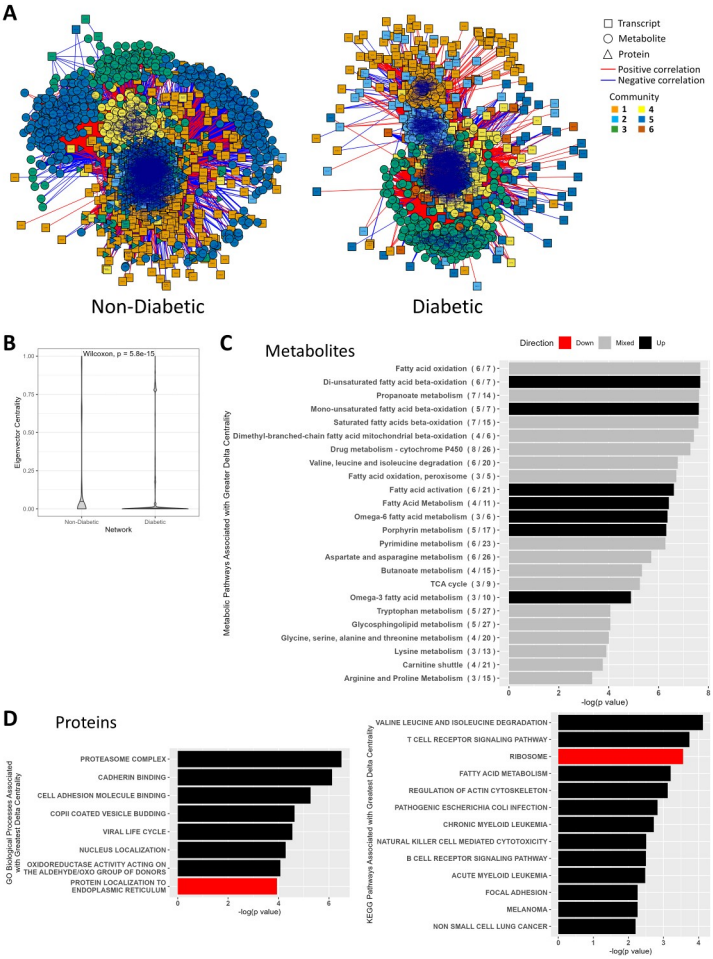

Figure 4. Differential network analysis of integrated transcriptomics, metabolomics, and proteomics data from islet cells of diabetic vs non-diabetic donors

A) Networks of associated metabolites (circles), transcripts (squares), and proteins (triangles) in islet cells from non-diabetic donors (left) and donors with T2D (right). Node colors represent communities of the most closely related omics features, and edge colors represent the direction of correlation between individual nodes. **B)** Violin plot representation of eigenvector centrality scores for features included in the non-diabetic and diabetic networks, with comparison by Wilcoxon rank sum test. Higher eigenvector centrality scores are assigned to features with greater connectivity within the network, i.e. a feature whose abundance correlates with the abundance of many other features which in turn correlate with the abundance of many other features. **C)** Metabolic pathways enriched in metabolites with a difference in eigenvector centrality > |0.1| between diabetic and non-diabetic networks, indicating pathways differentially prominent within the networks. Pathway p values assigned by mummichog algorithm take into account the number of differentially abundant features assigned to a pathway relative to the total number of features in the data set assigned to that pathway [(# differentially abundant features / # total features)]. Only pathways with $p<0.05$ and at least three features assigned to them which were differentially abundant between the two groups were considered. Black bars indicate that pathways were enriched in putative metabolites with higher centrality in the diabetic network. Gray bars indicate that a mixture of putative metabolites with centrality > 0.1 and centrality < -0.1 in the diabetic network were assigned to that pathway. **D)** GO Biological Processes and KEGG Pathways enriched in proteins with a difference in eigenvector centrality > |0.1| between diabetic and non-diabetic networks (FDR-adjusted $p<0.1$), derived from GSEA against gene sets in the HMSD. Proteins were ranked by the difference in their eigenvector centrality score between the diabetic and non-diabetic network. Red bars indicate Processes/Pathways with ES less than zero, indicating their enrichment in proteins with lower centrality in the diabetic network, suggesting less influence in the system, whereas those with ES greater than

zero – indicating higher centrality in the diabetic network and greater influence in diabetic islets – are depicted in black.