UNIWERSYTET MEDYCZNY W ŁODZI | BTM | International Doctoral School, Medical University of Lodz

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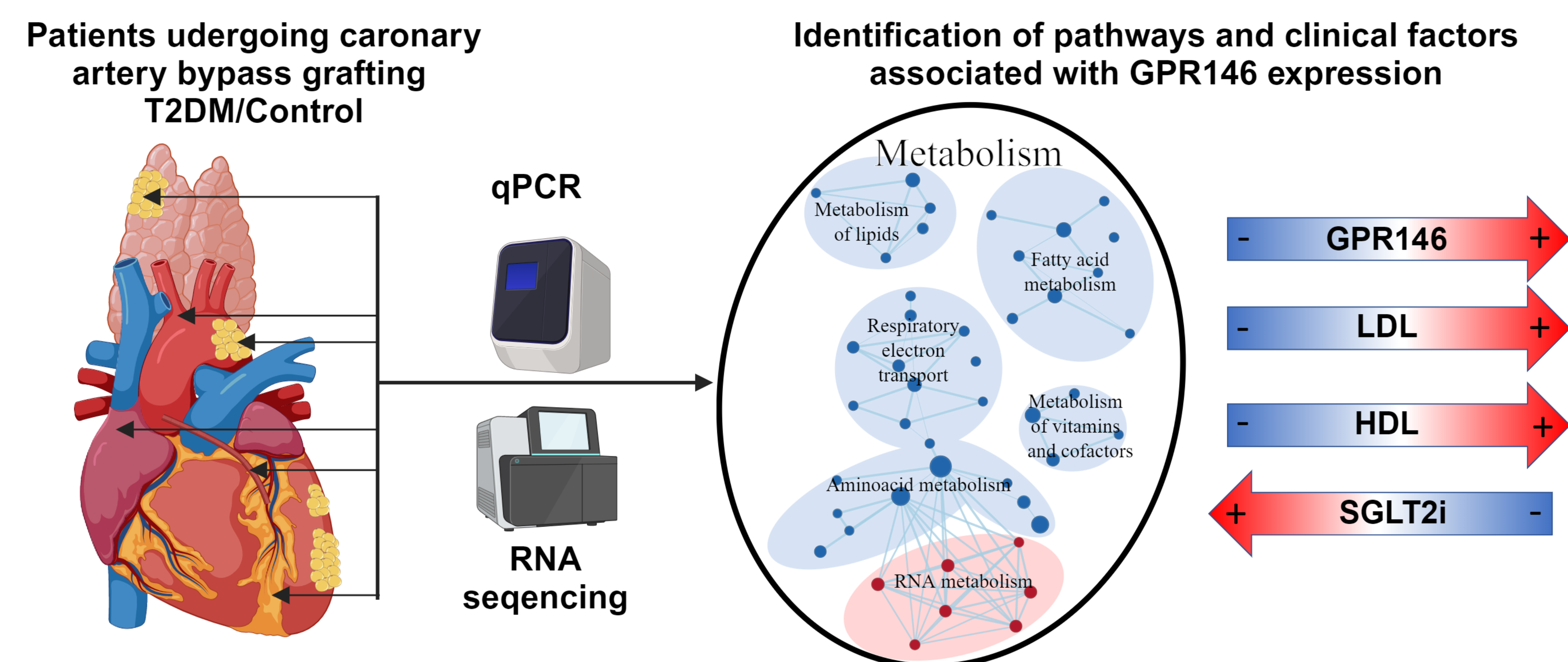
The role of GPR146-dependent signalling pathways in lipid metabolism

Background & Aims

- G-protein coupled receptor 146 (GPR146) was long considered a candidate receptor for proinsulin C-peptide (1), however, recently it has been proven to respond to a newly discovered hormone – cholesin (2).
- This ligand-receptor pair was shown to play a crucial role in hepatocyte lipid metabolism, namely to inhibit cholesterol synthesis in response to intestinal cholesterol absorption (2). This recent discovery indicated GPR146 as a promising therapeutic target against atherosclerosis.
- However, the understanding of signalling pathways downstream of the receptor is still very limited as well as its role in tissue types other than hepatocytes.
- The aim of this study was to investigate GPR146-associated pathways in cardiovascular-associated adipose tissues and to analyse the effect of diabetes and its treatment with SGLT2 inhibitors (SGLT2i) on these pathways.

Methods



- **Recruited patients:** Adults with type 2 diabetes (T2DM) or without diabetes (control group) qualified for elective coronary artery bypass grafting (CABG). Tissue samples including **fragments of aorta, saphenous vein, right atrial appendage, periaortic (PAT), epicardial (EAT) and thymic (TAT) adipose tissues** were extracted during CABG procedure by a cardiosurgeon.
- **qPCR:** GPR146 expression was measured at mRNA level (RT-PCR, RNaeasy Mini Kit, Qiagen, Germany, GAPDH-reference gene) in collected tissues.
- **RNAseq:** RNAseq was performed with NextSeq 500/550 High Output Kit v2.5 (300 Cycles; Illumina, California, USA). Geneset enrichment analysis (GSEA) was used to investigate pathways and genes coexpressed with GPR146.

Results

46 participants were included to the study [37 male, 23 with type 2 diabetes, median age 68.50 (Q1-Q3: 63.00-72.00) years, BMI 28.39 (26.06-31.49) kg/m2. GPR146 mRNA level (qPCR) was measured in all 6 types of tissues. It significantly correlated with BMI and serum concentrations of total cholesterol and LDL in adipose tissues in T2DM subgroup and with C-peptide in thymic adipose tissue in total group of patients (**Figure 1**).

	Total EAT	Total TAT	Total PAT	T2DM EAT	T2DM TAT	T2DM PAT	Control EAT	Control TAT	Control PAT
LVEF [%]	0.03	-0.05	-0.17	-0.03	0.08	-0.15	0.20	-0.15	0.25
BMI [kg/m2]	0.28	0.21	0.29*	0.47*	0.51*	0.34	0.14	0.01	-0.16
C-peptide [nmol/l]	-0.07	0.33*	0.00	0.11	0.41	0.13	-0.26	0.23	0.24
HbA1c [mmol/mol]	0.14	-0.06	0.16	0.07	0.02	0.01	0.04	-0.10	-0.10
Triglicerides [mmol/l]	-0.07	-0.02	-0.14	0.12	0.20	0.23	-0.28	-0.31	-0.58*
Total cholesterol [mmol/l]	0.20	0.28	0.18	0.50*	0.26	0.55*	0.00	0.24	-0.30
LDL [mmol/l]	0.07	0.15	0.10	0.47*	0.28	0.63*	-0.24	0.01	0.10
HDL [mmol/l]	0.09	-0.03	0.10	0.22	-0.08	0.10	0.19	0.00	-0.20

Spearman Rho: 0.5 / 0 / -0.5

Figure 1. GPR146 mRNA level significantly correlated with BMI and serum concentrations of total cholesterol and LDL in adipose tissues.

RNAseq was carried out on a subset of patients (T2DM N=5, control N=5) in two tissue types (EAT and TAT). Pathways associated with GPR146 expression were determined with GSEA. Results showed a significant correlation between GPR146 mRNA expression and metabolic pathways (**Figure 2**).

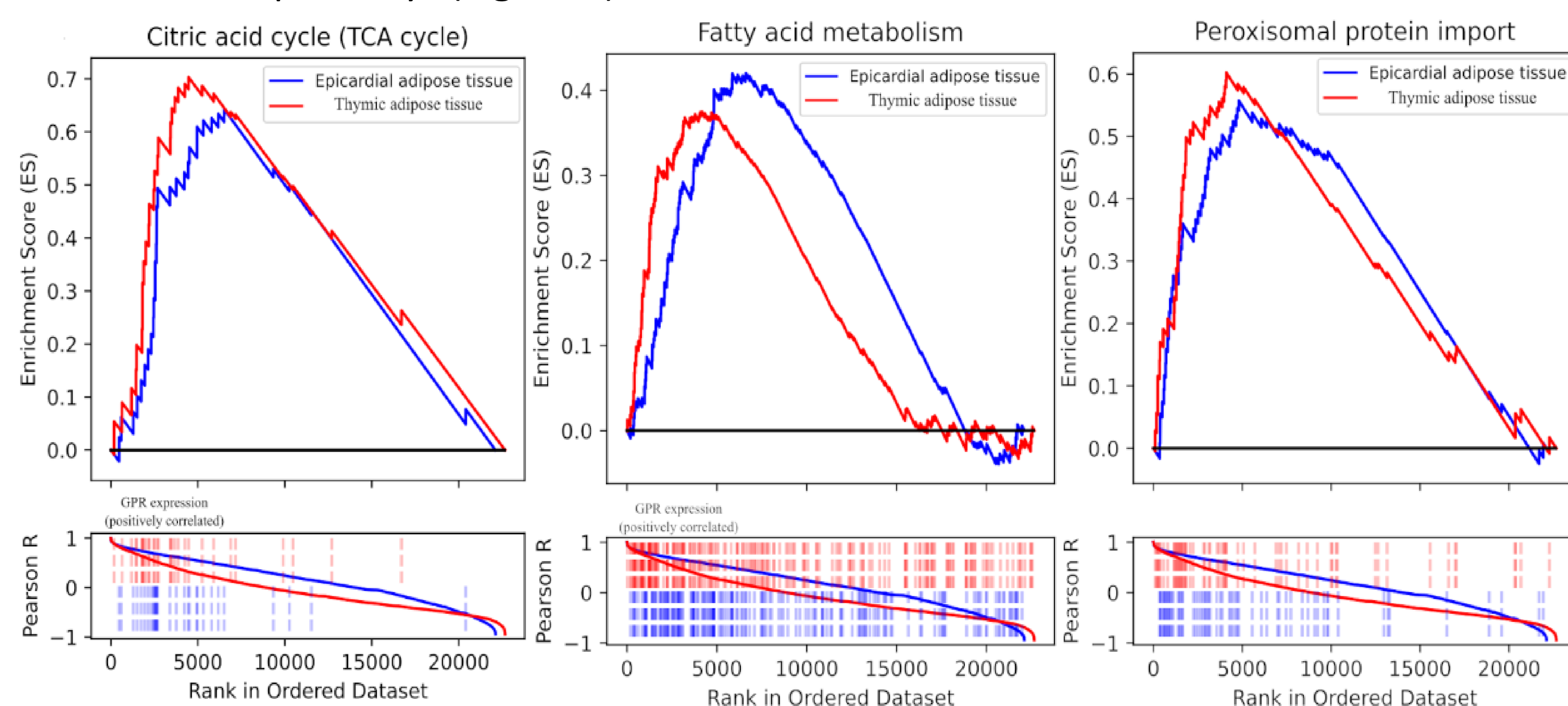


Figure 2. Enrichment plots of selected genesets enrichment in EAT (blue) and TAT (red): citric acid TCA cycle, fatty acid metabolism and peroxisomal protein transport pathways.

Individual genes coexpressed with GPR146 were identified ((|R|>0.75 in both EAT and TAT) (**Figure 3**). This geneset showed a significant, positive correlation with serum concentration of LDL, HDL and total cholesterol. Interestingly, SGLT2i treatment was associated with significant downregulation of GPR146-associated geneset, specifically in EAT. SGLT2i exposure affected the transcriptomic profiles in EAT and showed a significant down-regulation of pathways associated with peroxisomal metabolism and IGF1 signaling (**Figure 4**). In addition, geneset expression patterns associated with SGLT2i were inverse to those significantly correlated with GPR146 expression, HDL and total cholesterol levels.

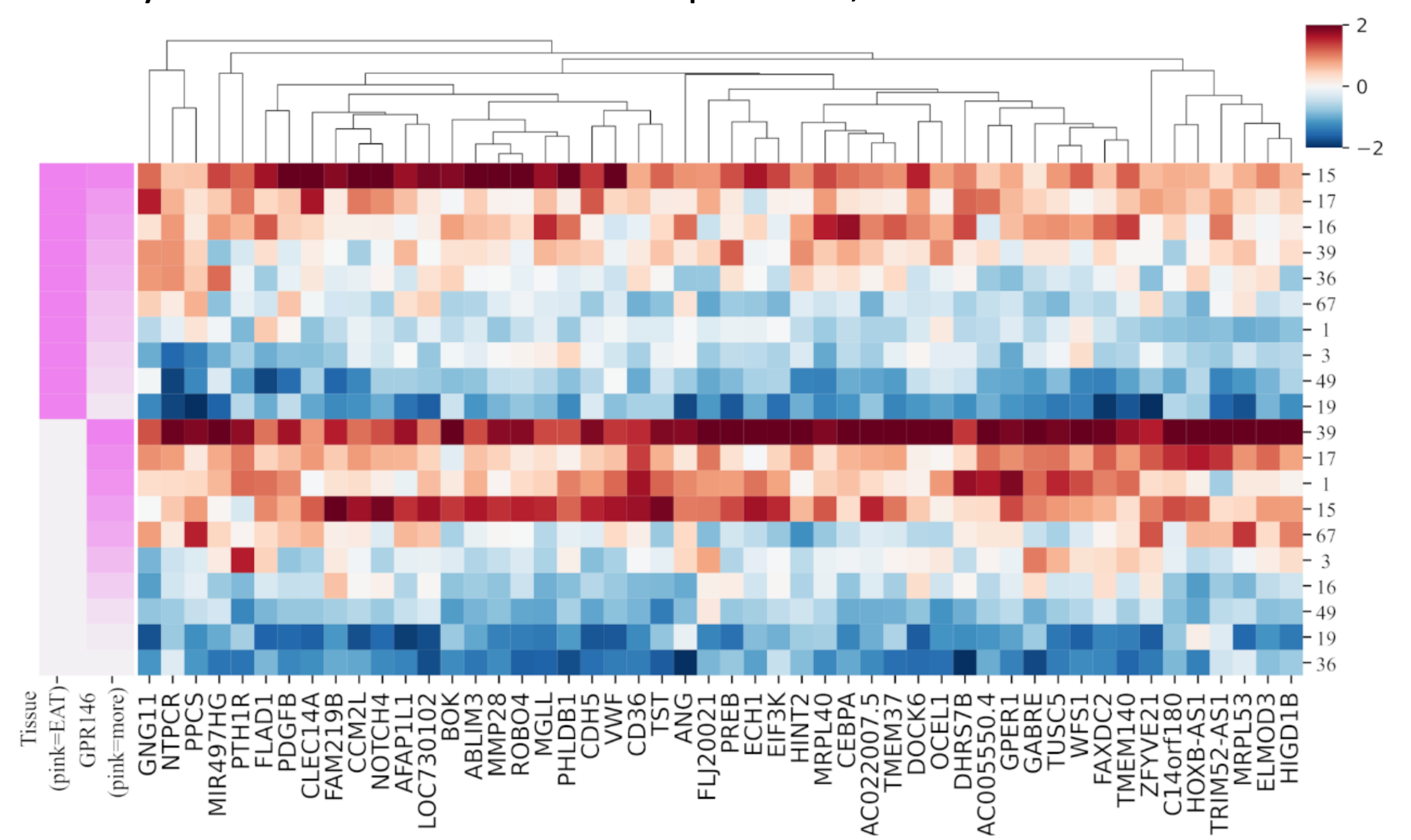


Figure 3. Heatmap of 50 genes with the strongest correlation in both EAT and TAT with GPR146 levels.

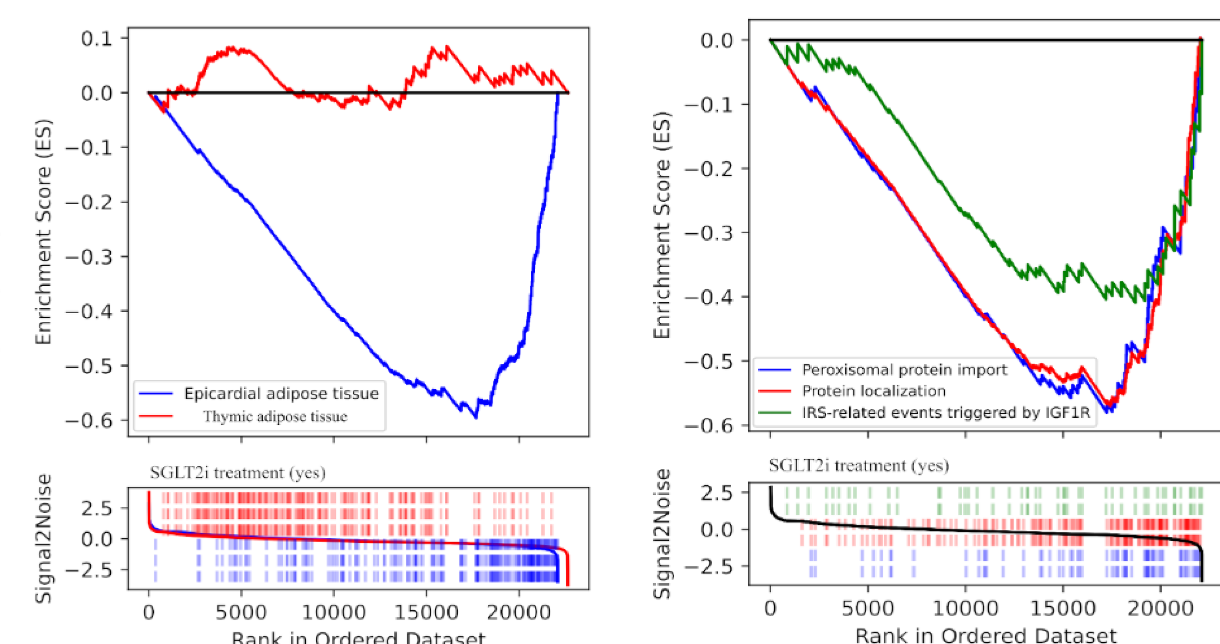


Figure 4. Enrichment plot of the GPR146-associated geneset showed significant downregulation in SGLT2i-treated individuals in EAT (left). Enrichment plot of significant suppression of peroxisomal metabolism (blue and red) and insulin-like growth factor-1 (green) signaling pathways in EAT in individuals treated with SGLT2i.

Conclusions

The results of our study suggest that GPR146 is metabolically active in cardiovascular-associated adipose tissues and GPR146-dependent signaling pathways may be suppressed with SGLT2i treatment. The results presented on this poster are currently under review in Cardiovascular Diabetes journal.

References

1. Yosten G, Kolar G, Redlinger L, Samson W. Evidence for an interaction between proinsulin C-peptide and GPR146. The Journal of endocrinology. 2013; B1-8, 218(2).
2. Hu X, Chen F, Jia L, Long A, Peng Y, Li X, et al. A gut-derived hormone regulates cholesterol metabolism. Cell. 2024; 187(7):1685-1700.e18.

Acknowledgements