Role of thiazolidinediones in adipose tissue remodeling

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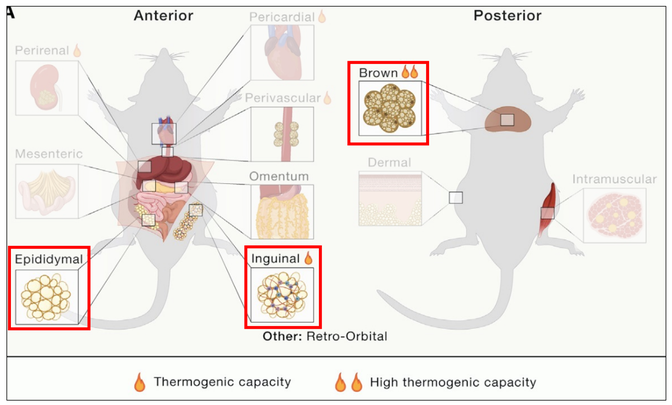
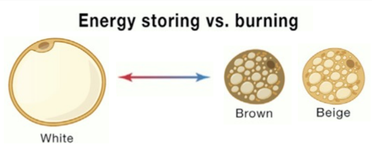
Abstract

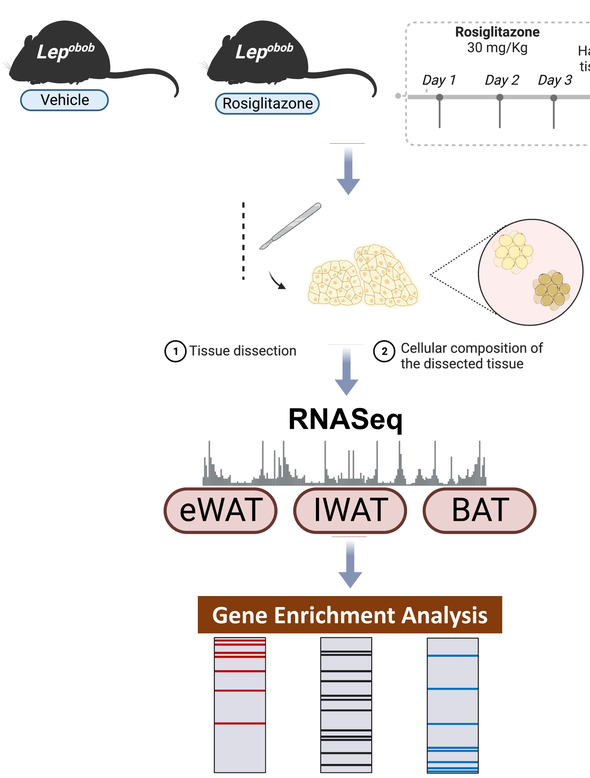
Adipose tissue is a plastic and heterogeneous tissue involved in many metabolic processes such as insulin response, food intake, energy storage and thermogenesis. It is also involved in several diseases such as diabetes, cardiovascular disease, and obesity. There are three types of adipocytes: white, beige, and brown; white functions for energy storage while brown and beige, for thermogenesis. PPAR-γ is a major transcription factor that is highly expressed in adipocytes. Activation of PPAR-γ by thiazolidinediones has a significant antidiabetic response; however, the detailed mechanism of action is still unclear. RNA-Seq analysis of brown, epidydimal and inguinal adipose tissue was performed on a genetic mouse model of obesity (type 2 diabetes) after treatment with the Pparg agonist, rosiglitazone. We observed a greater number of overlapping genes between brown and inguinal. For the downstream analysis, we focused on the overlapping upregulated genes from the three tissues because it provides a common rosiglitazone-driven remodeling. We found that within this list of genes the oxidoreductase, carboxylic acid metabolism and Pparg signaling pathways were enriched. Recognizing the pathways with the highest relevance to different processes occurring within the adipose tissue will allow us to understand the mechanisms by which rosiglitazone and other TZDs work as antidiabetic drugs and help combat obesity.

Background





Methodology



Gene overlap and enrichment analysis in the PPAR-γ inducing system

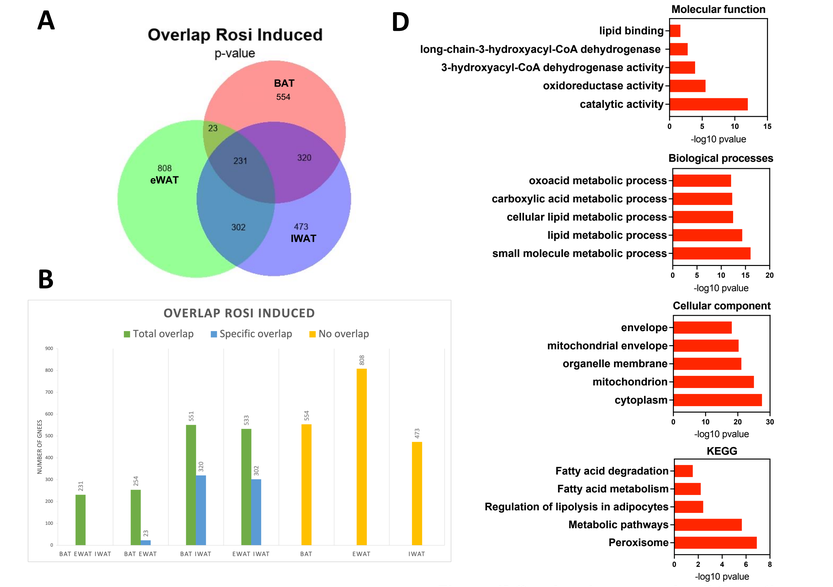


Figure 1] Overlapping genes in all three tissues and enriched pathways from the GSEA. (A) Overlapping genes and number of genes that are upregulated exclusively in eWAT, IWAT and BAT when the PPAR-γ pathway has an inducing effect.**(B)** Comparison of the number of genes that overlap including the specific and total overlap between each of the tissues. **(C)** Image from the GSEA of all the enriched pathways in the induced system. **(D)** Graphs of the 5 enriched pathways with the highest relevance within a particular mechanism.

Gene overlap and enrichment analysis in the PPAR-γ repressing system

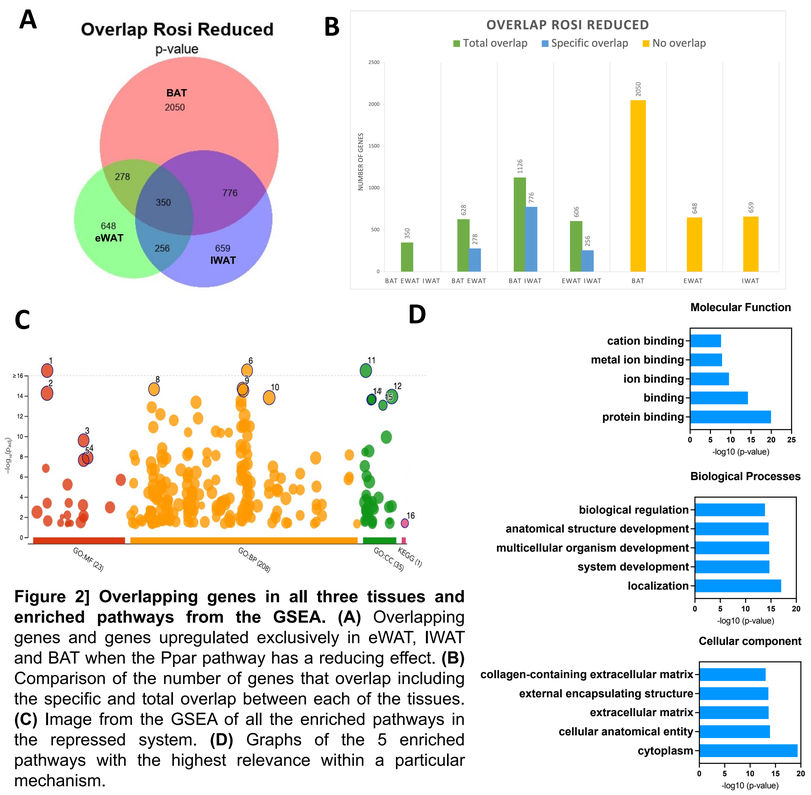


Figure 2] Overlapping genes in all three tissues and enriched pathways from the GSEA. (A) Overlapping genes and genes upregulated exclusively in eWAT, IWAT and BAT when the Ppar pathway has a reducing effect. **(B)** Comparison of the number of genes that overlap including the specific and total overlap between each of the tissues. **(C)** Image from the GSEA of all the enriched pathways in the repressed system. **(D)** Graphs of the 5 enriched pathways with the highest relevance within a particular mechanism.

Gene enrichment analysis for the PPAR-γ induced system with full change value of 1.7

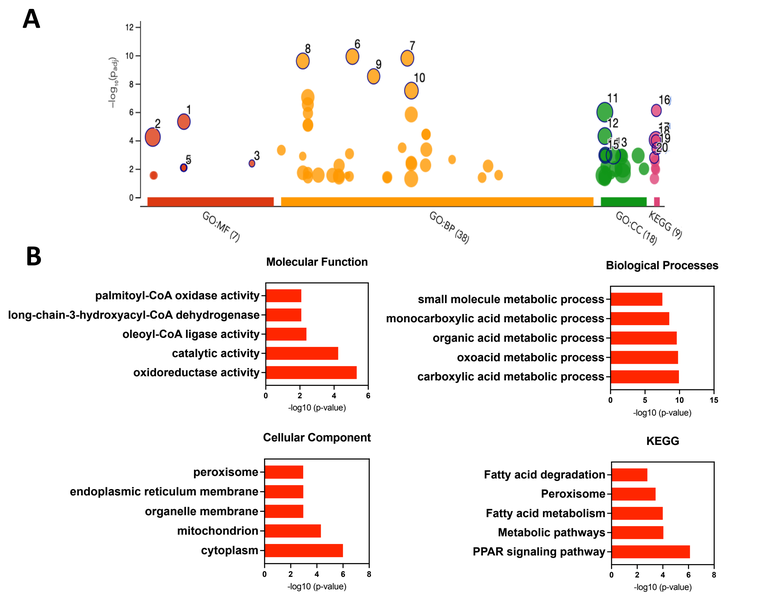


Figure 3] Enriched pathways of the genes that are significant within the full change (A) Image of Gene enrichment analysis that shows all the enriched pathways in the induced system, applying a cutoff value of 1.7. **(B)** Graphs of the 5 enriched pathways with the highest relevance.

Conclusions

- The total overlap between all three tissues increases in the repressed system. There is a significant overlap between BAT/IWAT compared to BAT/EWAT in both systems.
- By changing the p-value cutoff, a shorter list of genes was obtained which helped determine more specific pathways that are enriched with the PPAR agonist.
- The PPAR signaling pathway is the most relevant pathway in the KEGG database when the cutoff value is applied to the Gene enrichment analysis.
- This project lets us know what processes are relevant and can become targets for future treatments of different metabolic diseases.
- Recognizing the enriched pathways that PPAR-γ induces we can determine different ways to combat metabolic diseases such as obesity and diabetes.