Task1

1. Medically relevant insight from the article

The study demonstrates that subcutaneous white adipose tissue (WAT) in obese humans displays selective insulin resistance. Specifically:

Insulin-induced expression of genes involved in lipid and cholesterol biosynthesis is preserved in obesity.

In contrast, insulin regulation of genes related to tissue remodeling and protein translation (ribosome biogenesis) is markedly attenuated in obesity.

After major weight loss (e.g., post-bariatric surgery), insulin responsiveness of most pathways is restored to the level of non-obese subjects, and some pathways (e.g., one-carbon metabolism) are even more strongly regulated in formerly obese women.

Clinical implication: Adipose insulin resistance is not uniform but pathway-specific, with energy storage pathways spared while remodeling functions are impaired. This selective resistance may contribute to ectopic lipid deposition and metabolic disease risk. Importantly, substantial weight loss can largely reverse these defects

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2. Genomics technologies used

Cap Analysis of Gene Expression (CAGE): High-resolution mapping of RNA 5′ ends to quantify promoter activity and assess insulin-regulated transcription at the promoter level.

Differential expression analysis: Using edgeR to identify significant changes (FDR < 0.05).

Pathway and motif enrichment: clusterProfiler for functional enrichment; LOLA and UniBind for transcription factor binding site enrichment (showing roles of PPARγ, C/EBPβ, SREBP, LXR, etc.).

Clinical phenotyping: Hyperinsulinemic–euglycemic clamp to measure systemic insulin sensitivity, linked with transcriptional profiles

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3. Further related research questions and hypotheses

Mechanism of selective insulin resistance:

Why are lipogenic gene responses preserved while remodeling and translation pathways are blunted in obesity?

Hypothesis: Divergent downstream signaling branches (e.g., mTORC1 vs FOXO) or chromatin accessibility differences underlie this selectivity.

Functional role of ribosomal gene repression:

What is the biological significance of coordinated ribosome downregulation in lean subjects?

Hypothesis: It alters translational selectivity, shifting adipocyte metabolism and protein synthesis priorities.

Enhanced one-carbon metabolism after weight loss:

Does the strengthened insulin response in one-carbon metabolism in post-obese subjects contribute to long-term metabolic reprogramming?

Hypothesis: Increased methyl-donor availability may reset the adipocyte epigenome, stabilizing restored insulin sensitivity.

Circadian regulation and TGF-β signaling:

How does the blunted insulin regulation of circadian clock genes in obesity affect feeding-related metabolic rhythms?

Hypothesis: Impaired insulin entrainment of clock genes contributes to metabolic desynchrony, exacerbating insulin resistance.

Transcription factor network switching:

How do promoter contexts dictate the shift from “common” TFs (PPARγ, C/EBPβ) to those weakened in obesity (AR, GR) or strengthened post-obesity (EBF1, ESR1, SMAD3)?