**Polygenic risk scores and gene expression patterns link developmental preadipocyte marker genes to age-obesity interactions**

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**REFERENCES**


**BACKGROUND**

- **Adipogenesis** is the process during which fat cells develop by differentiation from preadipocytes
- At the genetic level, transcription factors such as PPARy and CEBP regulate differentiation
- *Aging* and *Obesity* both result in:
  - Impaired adipogenesis → inflamed, dysfunctional adipocytes
  - Altered expression of differentiating factors and their co-regulators
  - Most studies focus on either age or obesity; interactions between obesity and aging are largely unexplored

**METHODS**

1) **Gene Identification**
   - Use adipose snRNA-seq to identify and test unique preadipocyte marker genes for differential expression (DE) by age in preadipocytes
2) **Functional Analyses**
   - Examine genes DE by age for enrichment of biological processes and functional pathways using Webgestalt
3) **Regional Polygenic Risk Scores**
   - Perform non-age adjusted GWAS for BMI
   - Construct polygenic risk score (PRS) models using GWAS summary statistics of variants within ~500 kb of genes (Regional PRS)
   - Assess significance of reported coefficients in model: BMI ~ Age + PRS + PRS:Age
4) **Longitudinal DE Analyses**
   - Perform DE analyses on genes using adipose bulk RNA seq-data across 14 days over 6 timepoints from adipogenesis cell-line experiment

**RESULTS**

- 50 preadipocyte marker genes are DE by age in preadipocytes
- 48 out of 50 are upregulated in preadipocytes with age

**DE Genes are enriched for developmental processes**

- 8 out of top 10 pathways are related to development or differentiation
- Regulation of cell differentiation ranks first in significance

**DISCUSSION**

- 50 developmental preadipocyte marker genes are involved in the aging process in adipose tissue
- Most of their expression levels increase with age
- Different patterns of gene expression during and after adipogenesis can suggest these genes play many roles in fat cell production
- Similar peaks in impulse-models suggest genes are in common pathways, coexpressed, or regulated by same TFs
- Obesity affects these genes → disruption in aging
  - In obese individuals, variants nearby these genes notably interact with age to reduce BMI
  - This contrasts what is typically observed - most variants usually interact with age in lean individuals

**REFERENCES**


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