Title:
In silico screen identifies candidate drugs that induce differentiation of adipose progenitor cells into beige adipocytes.

Author:
Sam D. Chorlton* (1)

Affiliation:
(1) Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada

Background:
Beige adipocytes, a specialized cell type that dissipate energy to produce heat, play an important role in the regulation of energy balance. Recent evidence suggests that physiologic growth of beige adipocyte populations derives from differentiation of adipose progenitor cells (1). Stimulating the generation of new beige adipocytes could present an effective means to combat obesity and other metabolic disorders. In this work, I perform an in silico screen of 2331 approved and investigational drugs that may induce differentiation of adipose progenitor cells into beige adipocytes.

Methods:
Methods for recombinant expression of PGC-1a in bone-derived mesenchymal stem cells (BMSCs), RNA isolation and microarray hybridization have been previously described (2). For LINCS signature generation, raw microarray data was fRMA processed and confounding variables identified using Surrogate Variable Analysis. Differential expression was calculated with the limma R package and gene set enrichment was performed with DAVID. Only the adipose-derived stem cell line in the Library of Integrated Cellular Signatures (LINCS) was queried.

Results:
Of the 10 638 probesets measured in the LINCS database, 49 were upregulated and 38 were downregulated in the PGC-1a expressing BMSCs compared to control BMSCs. Gene set enrichment of the upregulated genes revealed significant enrichment of cellular component term “mitochondrion” (p=6.14×10-7) and biological process terms “tricarboxylic acid cycle” (p=8.47×10-5) and “acetyl-CoA catabolic process” (p=8.47×10-5). Compared with two other published models of brown adipocyte differentiation (3,4), 26/34 (76%, cumulative binomial p=0.001) RNA transcripts and 37/54 (68%, cumulative binomial p=0.004) genes show concordant direction of fold change, confirming the reproducibility of the differentially expressed genes.

Conclusions:
LINCS, a database of drug-induced gene expression changes, was queried to find drugs that induce a transcriptional change similar to the differentiation of BMSCs into beige adipocytes.

The top ranked drugs include SYK-inhibitor and ruxolitinib, a JAK inhibitor, which have both been shown to induce browning of white adipocytes (4).

References:

1. Wang QA, Tao C, Gupta RK, Scherer PE. Tracking adipogenesis during white adipose tissue development, expansion and regeneration. Nat Med. 2013 Sep 1;19(10):1338-1344. Pubmed PMID: 23995282.

2. Huang P-I, Chen Y-C, Chen L-H, Juan C-C, Ku H-H, Wang S-T, et al. PGC-1α mediates differentiation of mesenchymal stem cells to brown adipose cells. J Atheroscler Thromb. 2011;18(11):966–80. Pubmed PMID: 21817823.

3. Karbiener M, Pisani DF, Frontini A, Oberreiter LM, Lang E, Vegiopoulos A, et al. MicroRNA-26 family is required for human adipogenesis and drives characteristics of brown adipocytes. Stem Cells Dayt Ohio. 2014 Jun;32(6):1578–90. Pubmed PMID: 24375761.

4. Moisan A, Lee Y-K, Zhang JD, Hudak CS, Meyer CA, Prummer M, et al. White-to-brown metabolic conversion of human adipocytes by JAK inhibition. Nat Cell Biol. 2015 Jan;17(1):57-67. Pubmed PMID: 25487280.