p53 regulates the lipid metabolism response to metabolic stress in brown adipose tissue

Background
Introduction: Obesity and metabolic dysfunction are highly prevalent worldwide and are associated with increased risk for type 2 diabetes and cardiovascular disease. Brown adipose tissue (BAT) possesses significant potential due to its ability for uncoupled respiration and is investigated as a therapeutic target. In addition to its role as a thermoregulator, p53 is described as a regulator of metabolism in non-transformed cells, and the role of p53 in nutrient flux regulation of adipose tissue is not well understood.

Methods: Acute, BAT-specific p53 knockout (BKO) mice were generated using the tamoxifen-inducible CreER<sup>T2</sup>-LoxP system. Control and BKO mice were subjected to fasting or refeeding to investigate the functional role of p53 in directing brown adipocyte nutrient oxidation.

Results: BKO mice demonstrated altered lipid metabolism in BAT and, unexpectedly, also in white fat. Furthermore, the response to acute adrenergic stimulation was blunted in BKO mice, which displayed altered systemic triglyceride metabolism and lipid mobilisation.

Conclusions: Taken together, these data suggest that p53 is an integral part of acute lipid metabolism regulation in BAT. Further investigation will be important in understanding the implication of p53 in nutrient turnover in the context of obesity and metabolic stress.

Knockout model and study design

Metabolic gene expression profile

Fig. 4: Altered BAT gene expression profile in p53BKO. Expression of genes regulating (A) glucose-related processes and (B) lipid metabolic processes in BAT. Data expressed as mean ± SEM, n=6. Mann-Whitney test, *p<0.05.

p53 mediates beta-adrenergic response

Administration of beta 3-adrenergic agonist, CL316,243, in mice lacking Trp53 in brown adipocytes disrupts systemic lipid metabolism

Fig. 5: Lipid metabolism is altered after beta-adrenergic stimulation in p53BKO. Circulating (A) glucose, (B) glycerol, (C) free fatty acids and (D) triglycerides at baseline, 20, 40, 120, 180 minutes after CL316,243 injection (10<sup>−5</sup> μg/kg). (E) Circulating triglyceride levels, calculated as AUC (0-180 min). (F) Expression of genes regulating lipid uptake in BAT. Data expressed as mean ± SEM, n=5. Multiple transrs or Mann-Whitney test. AUC, area under the curve.

Loss of p53 in brown adipocytes disrupts energy metabolism

Fig. 6: Markers of beta-adrenergic stimulation. (A) Expression of Ucp1 and Adrb3 in BAT. (B) UCP1 protein levels in BAT. Data expressed as mean ± SEM, n=5. Mann-Whitney test.

Summary
- Acute, brown adipocyte-specific ablation of p53 generates a hypermetabolic state by inducing carbohydrate metabolism and energy expenditure
- Gene expression analysis indicates alterations in nutrient pathways following acute loss of p53 in brown adipocytes
- p53 mediates lipid metabolism in response to beta-adrenergic stimulation in BAT, possibly via triglyceride uptake modulation