Nutrients, control of gene expression and metabolic homeostasis
Lipid metabolic enzymes: emerging drug targets for the treatment of obesity

- Obesity
- Type 2 diabetes
- Insulin resistance
- Dyslipidaemia
- Hypertension
- Coronary heart disease
- Stroke
- Gallbladder disease
- Sleep apnoea
- Osteoarthritis
- Hyperuricaemia
- Cancer

PPAR-mediated fatty acid control of mitochondrial fatty acid metabolism

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FGF21 expression is regulated by diet and its effects are widely distributed.
Fibroblast growth factor (FGF) 21 is a member of the FGF family, predominantly produced by the liver in response to the PPARα transcription factor, inducing adipose tissue lipolysis, liver ketogenesis, and metabolic adaptation to the fasting state.

FGF21 expression is induced by the 26S proteasome inhibitor MG132
Amino acid starvation (HisOH) induces FGF21 transcription

Graph A: Relative mRNA levels of FGF21 over time.

Graph B: Transcriptional activity of FGF21 over time.

Graph C: Western blot showing ATF4 and Actin levels with and without HisOH treatment.
FGF21 is an ATF4 target gene

**A**

<table>
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Consensus: 

**AARE1**

**AARE2**

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Consensus: 

**B**

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**C**

![Bar chart showing FGF21 promoter activity](image)

**D**

![Bar chart showing FGF21 promoter activity](image)
ATF4 binds to the FGF21 gene (ChIP analysis)
Effect of siRNA-mediated ATF knockdown on endogenous FGF21 expression
Leucine deprivation induces FGF21 serum levels and mRNA expression in liver
FGF21, the missing link between amino acid deprivation and lipid metabolism

FGF21 induces:
- gluconeogenesis
- fatty acid oxidation
- ketogenesis
- brown fat activation
- reduction in adipose tissue and body weight

FGF21: ADAPTATIVE STARVATION RESPONSE

LIVER:
- Inhibits Lipogenesis
- Induces mobilization of lipid stores
- WAT: Increases FAO gene expression
- Decreases Lipogenesis
- BAT: Increases UCP1 expression

Could be FGF21 the link between aminoacid deprivation and lipid metabolism response observed in liver, WAT, and BAT?
Leucine deprivation in FGF21 knockout mice
FGF21 is differently regulated by leucine deprivation in liver and adipose tissues.
FGF21 is required for (-)leu diet effects on body weight without affecting food consumption.
Leucine deprivation effects on white adipocytes size are FGF21 dependent.
Leucine deprivation effects on lipid metabolism in WAT are FGF21 dependent
FGF21-KO liver has impaired lipid metabolism in response to leucine deprivation.
FGF21-KO liver has impaired lipid accumulation in response to leucine deprivation.
FGF21 is required for inducing BAT activation during amino acid deprivation.
Working model of the FGF21 regulatory pathway under leucine deprivation
Generation and characterization of the Fgf21 liver-specific knockout mice
Experimental design

Fgf21 liver-specific knockout mice

LoxP mice

LPD: Low protein diet (5%)
CD: Control diet (20%)
FGF21 is induced by a LPD in liver but not in BAT or WAT, and this induction correlates positively with plasma concentration.
LPD increases ATF4 protein levels in liver
Fgf21 deficiency significantly attenuates weight loss under a LPD
Hepatic FGF21 is required for inducing thermogenic gene expression in scWAT under a LPD.
FGF21 plasma levels correlate negatively with protein intake in humans
Insulin Resistance is Attenuated by Sofrito Supplemented-Diet in OZR
FGF21 Serum Levels are not Influenced by Sofrito
FGF21 Signaling is Improved in vWAT of OZR Fed with a Sofrito-Supplemented Diet

![Graph showing FGF21 signaling in Obese Control and Obese Sofrito groups](image)
Sofrito Induces UCP1 Expression in the vWAT of OZR

- **Ucp1**
- **Prdm16**
- **Pparg**
- **Pgc1b**

**mRNA relative levels**

- **Obese Control**
- **Obese Sofrito**

# symbol indicates a significant difference between Obese Control and Obese Sofrito.
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