458 PM20D1 as a key enzyme for energy expenditure

Asset Overview

Product Type	Protein
Indication	Obesity and others (Diabetes)
Current Stage	Lead optimization
Target(MoA)	Peptidase M20 domain containing 1 (PM20D1)
Brief Description	The Spiegelman lab has discovered a secreted enzyme, peptidase M20 domain containing 1 (PM20D1), that plays a key role in augmenting energy dissipation in thermogenic adipocytes. PM20D1 is a bidirectional biosynthetic enzyme for a class of N-lipidated amino acids, the metabolites of which are endogenous uncouplers that regulate mitochondrial respiration. PM20D1 is highly enriched in thermogenic versus non-thermogenic adipocytes and promotes energy expenditure in vivo. Mice with increased circulating PM20D1 show augmented energy expenditure, blunted weight gain on high fat diet, and improved glucose homeostasis. Furthermore, direct treatment of adipocytes with N-lipidated amino acids, such as oleoylphenylalanine, increases oxygen consumption.
Organization	Dana-Farber Cancer Institute

Differentiation

□ **Increased PM20D1 administration augments energy expenditure**

- PM20D1 is a secreted enzyme that regulates N-acyl amino acids in vivo. N-acyl amino acids are endogenous metabolites that uncouple mitochondria., Increased PM20D1 or N-acyl amino acid administration augments energy expenditure
- Administration of either recombinant PM20D1 or its N-lipidated amino acid products as potential novel therapeutic strategies for augmenting energy expenditure in humans

□ **PM20D1 show blunted weight gain on high fat diet and improved glucose homeostasis**

- Administration of N-acyl amino acids to mice improves glucose homeostasis and increases energy expenditure
- The data identify an enzymatic node and a family of metabolites that regulate energy homeostasis. This pathway might be useful for treating obesity and associated disorders.
- We identified a secreted enzyme, peptidase M20 domain containing 1 (PM20D1), that is enriched in UCP1+ versus UCP1- adipocytes. We demonstrated that PM20D1 is a bidirectional enzyme in vitro, catalyzing both the condensation of fatty acids and amino acids to generate N-acyl amino acids and also the reverse hydrolytic reaction

458

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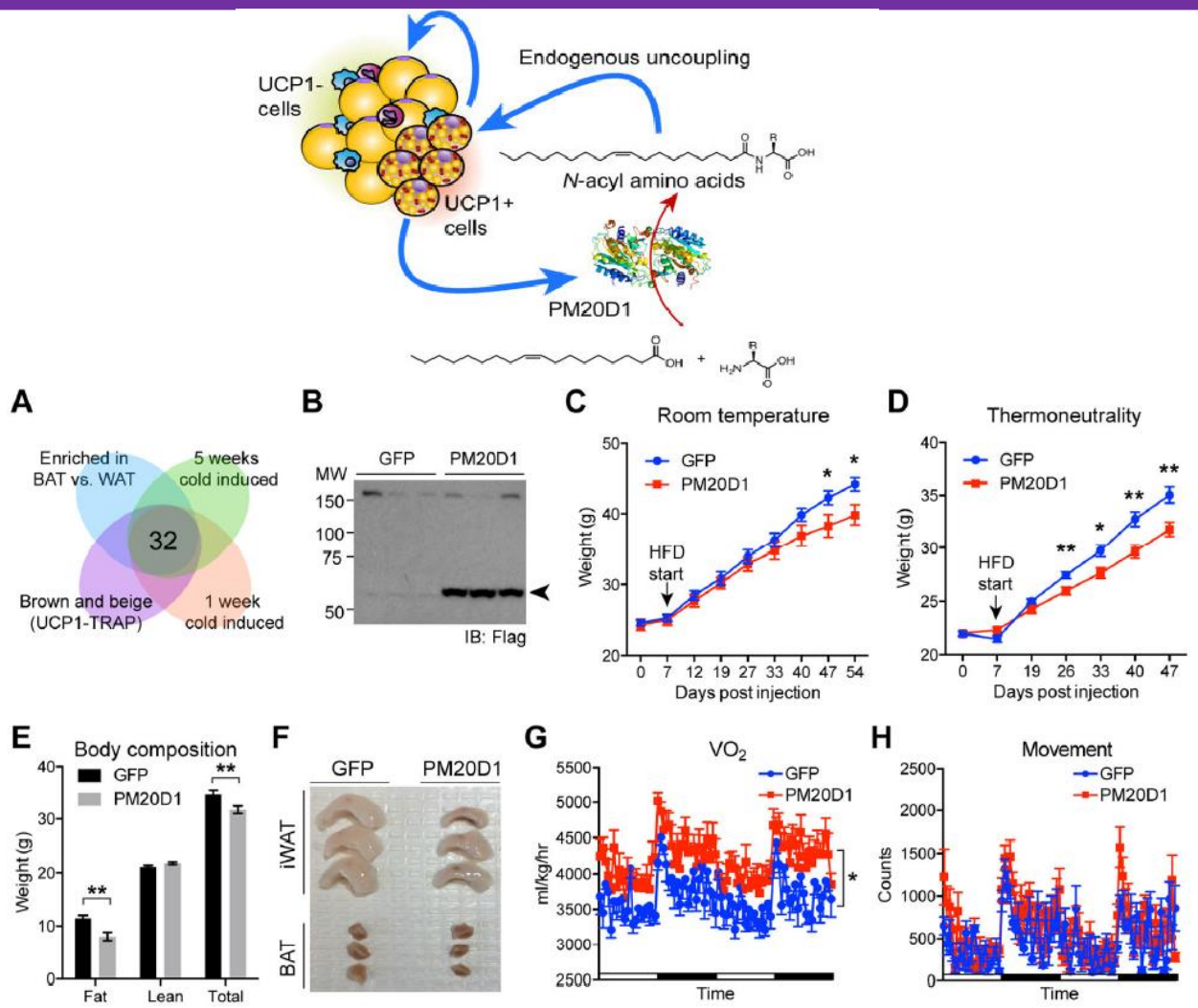
Key Data

Increased circulating PM20D1 augments whole body energy expenditure



(A) Schematic diagram of search strategy to identify factors expressed by UCP1+ cells. The following publicly available datasets were used for the comparisons: UCP1-TRAP, brown versus white adipose tissues (and inguinal fat following 1 or 5 weeks cold exposure (B and C) Anti-flag Western blot of plasma 40 days post injection (B) and whole body weight curves (C) from male C57BL/6 mice after tail vein injection of AAV-GFP or AAV-PM20D1 fed high fat diet (HFD). Mice were 7 weeks old at the time of injection, HFD was started 7 days post injection, and mice were maintained at room temperature for the duration of the experiment. (D), MRI analysis of total body composition (E), and representative images of adipose tissues (F) Mice were placed into thermoneutrality (30°C) at 6 weeks old, injected with virus at 7 weeks old, and HFD was started 7 days post injection. (G) and movement (H) of male C57BL/6 mice over a period of two days.

458

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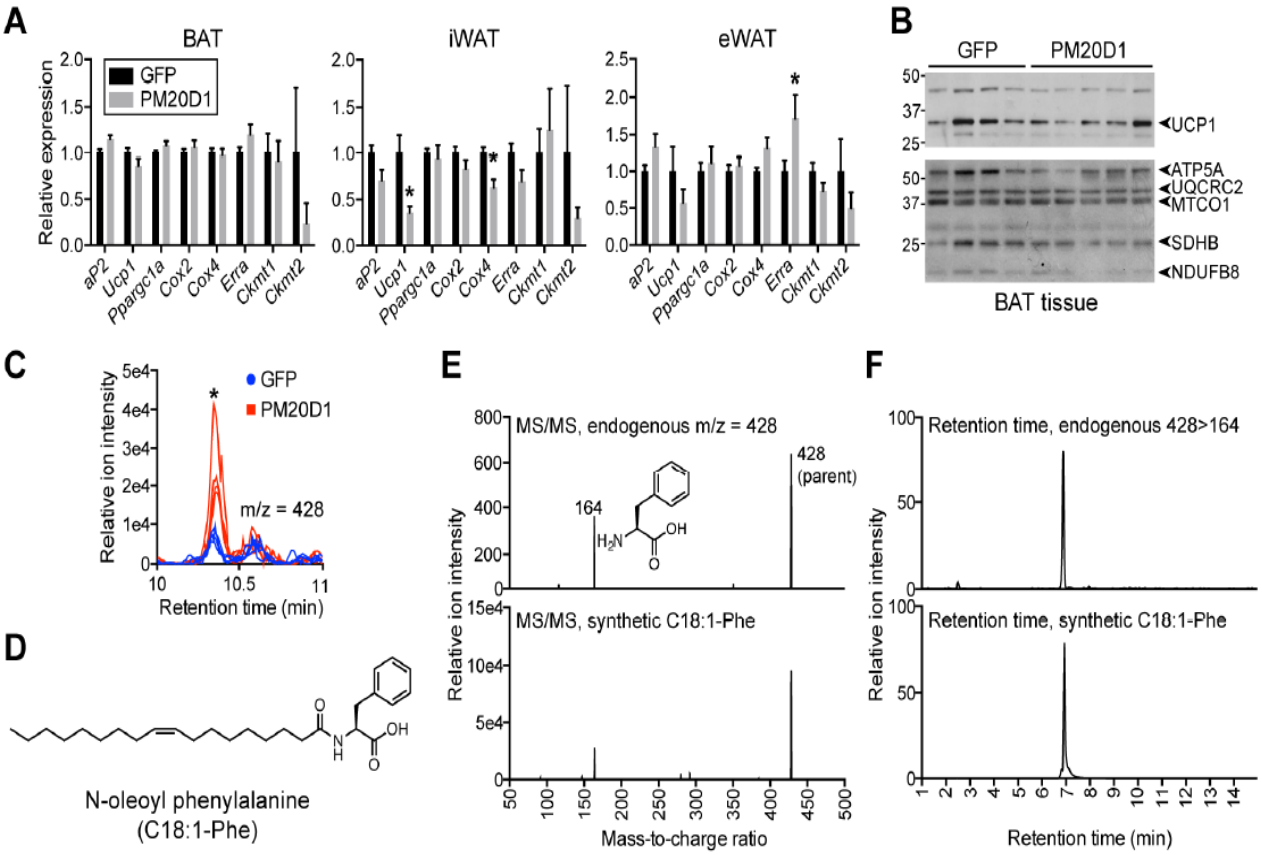
Lack of classical browning and identification of increased N-oleoyl phenylalanine in mice injected with AAV-PM20D1



(A and B) mRNA expression of the indicated genes in BAT, iWAT, and eWAT (A) and Western blot of UCP1 and mitochondrial proteins (B) from male C57BL/6 mice at thermoneutrality after tail vein injections of AAV-GFP or AAV-PM20D1. Mice were placed into thermoneutrality (30°C) at 6 weeks old, injected with virus at 7 weeks old, and high fat diet (HFD) was started 7 days post injection. Mice were maintained at 30°C for the duration of the experiment. (C) Chromatogram at m/z = 428 from plasma of male C57BL/6 mice after tail vein injection of AAV-GFP or AAV-PM20D1. For (C), mice were 7 weeks old at the time of injection, high fat diet (HFD) was started 7 days post injection, and mice were maintained at room temperature for the duration of the experiment. (D) Chemical structure of N-oleoyl phenylalanine (C18:1-Phe). (E and F) MS/MS spectra (E) and retention time (F) of endogenous (top) or synthetic (bottom) C18:1-Phe.

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Intellectual Property

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Country	US

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