Lunenfeld-Tanenbaum Research Institute
Sinai Health System

TECHNOLOGY TRANSFER & INDUSTRY LIAISON
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TECHNOLOGY ABSTRACT

Fibroblast Activation Protein (FAP) Knockout Mouse Model for Metabolic Research

Reference No.: INV-2026001

BACKGROUND

Fibroblast activation protein (FAP) is a serine protease closely related to dipeptidyl peptidase-4 (DPP-4) and has attracted interest as a potential therapeutic target in metabolic diseases, oncology, and fibrosis. Pharmacological inhibition of FAP has been reported to influence glucose metabolism and fibroblast-mediated processes, but inhibitor specificity and off-target effects remain concerns. Robust genetic models are therefore essential to clarify the biological role of FAP, validate drug mechanisms, and distinguish FAP-dependent from DPP-4-dependent effects. This FAP knockout mouse model was developed to address these needs by enabling definitive assessment of FAP function in vivo under both normal and metabolic stress conditions.

TECHNOLOGY OVERVIEW

The FAP knockout mouse model provides a genetic system for evaluating the biological role of fibroblast activation protein (FAP) in vivo, enabling characterization of FAP function across metabolic and disease-relevant contexts. The knockout is molecularly validated by genomic sequencing and functionally confirmed through the absence of FAP enzymatic activity in plasma and multiple tissues, including liver, pancreas, muscle, and adipose tissue. The model has been extensively phenotyped under both regular chow and high-fat diet conditions in male and female mice. Comprehensive metabolic testing demonstrates normal body weight regulation, glucose tolerance, insulin sensitivity, lipid handling, and energy expenditure in the absence of FAP. The model serves as a robust genetic control for validating FAP-targeted therapies and assessing target specificity. Beyond metabolism, the model can be employed for oncology, fibrosis, stromal biology, and inflammation research, where FAP expression in activated fibroblasts plays a critical role. The availability of a clean, well-characterized knockout provides a powerful platform for preclinical target validation and de-risking of therapeutic programs.

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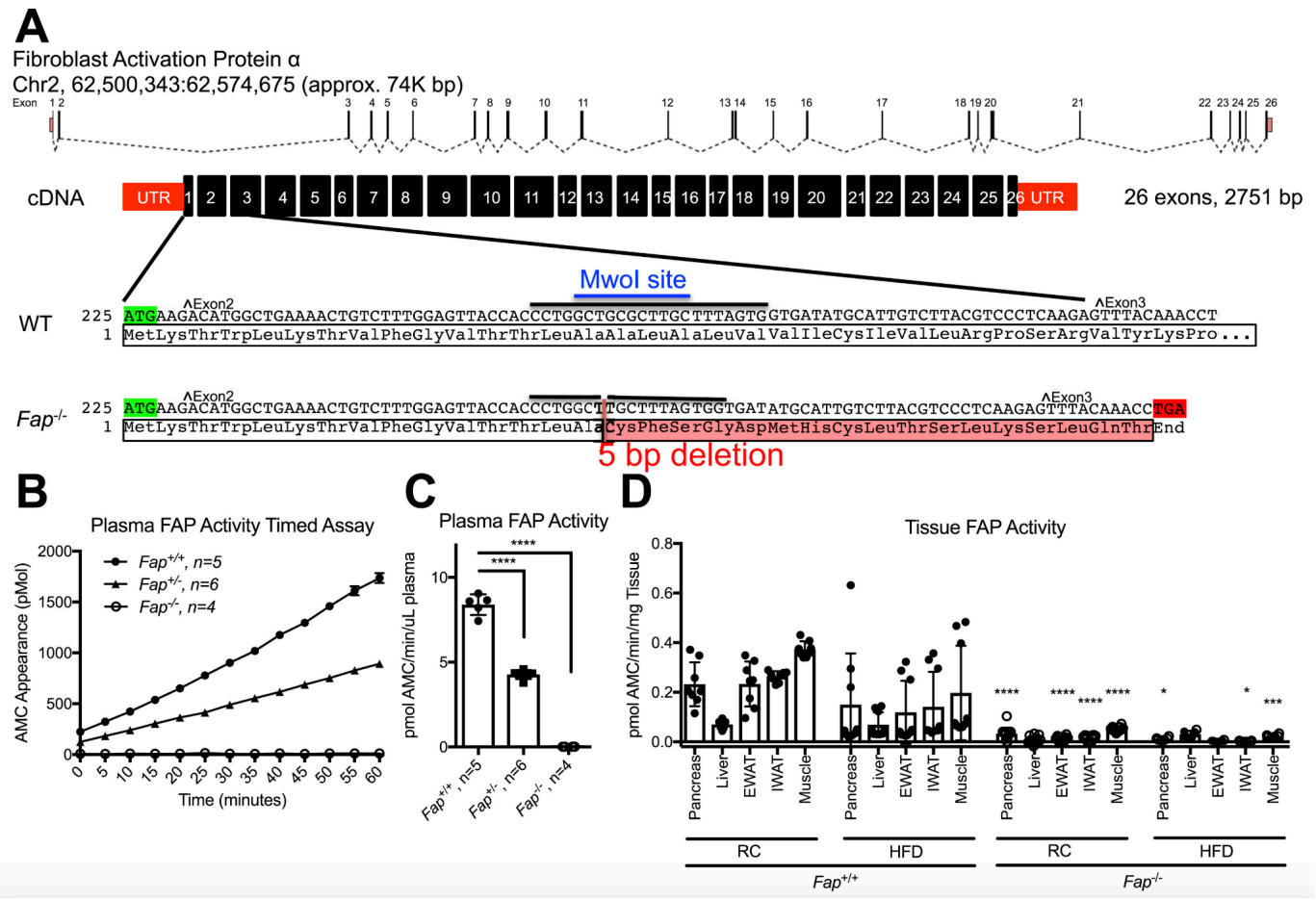

Figure 1. Generation and characterization of Fap−/− mice. A) A map of the FAP gene in mice and the partial cDNA sequence of wild-type and mutant Fap alleles are shown. The mutation causes a 5bp deletion and frame-shift occurring in exon 2 that is predicted to cause amino acid changes after Ala15 and an early truncation of the protein 17 amino acids later in exon 3. Start codon is in green; stop codons are in red. Black line indicates sequence targeted by guide RNA. ˆ indicates a new exon. B) AMC appearance over time during FAP activity assay in Fap+/+, +/−, −/− mice. C) Average FAP activity (slope analysis) over duration of FAP activity assay. D) FAP activity in various tissues from Fap+/+. Statistical significance was determined with ANOVA. *P < 0.05, ***P < 0.001, ****P < 0.0001, when compared to corresponding Fap+/+ control groups.

APPLICATION(S)

- Preclinical validation of FAP inhibitors and dual FAP/DPP-4 therapies
- Mechanistic studies of glucose homeostasis and metabolic regulation
- Cancer stromal biology and tumor microenvironment research
- Fibrosis and inflammatory disease modeling
- Comparative species studies of FAP biology

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COMPETITIVE ADVANTAGE(s):

- Definitive genetic ablation of FAP with validated loss of enzymatic activity
- Distinguishes on-target vs. off-target effects of FAP inhibitors
- Suitable for metabolic, oncology, fibrosis, and stromal biology studies
- Applicable across diet-induced and basal physiological conditions
- Reduces translational risk in drug discovery programs

RESEARCH TEAM:

- Daniel Drucker,
- Profiles of Daniel Drucker,
- Lab Website Drucker Lab

PUBLICATION:

https://pubmed.ncbi.nlm.nih.gov/30477988/

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