

GDF5 Promotes White Adipose Tissue Thermogenesis via p38 MAPK Signaling Pathway

Wenting Zhang¹, Xiaohui Wu², Zhou Pei¹, Wieland Kiess³, Yan Yang¹, Yong Xu⁴, Zhuo Chang¹, Jing Wu¹, Chengjun Sun¹, Feihong Luo¹

¹ Department of Pediatric Endocrinology and Inherited Metabolic Diseases, Children's Hospital of Fudan University, Shanghai, China; ² Institute of Developmental Biology and Molecular Medicine, School of Life Sciences, Fudan University, Shanghai, China; ³ Hospital for Children and Adolescent, University Hospitals, University of Leipzig, Leipzig, Germany; ⁴USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, USA

INTRODUCTION

Growth differentiation factor 5 (GDF5) was reported to regulate brown adipogenesis, however, its effects on insulin sensitivity, full metabolic syndrome spectrum and the thermogenesis in subcutaneous white adipose tissue (sWAT) haven't been elucidated yet.

RESULTS

Fabp4-GDF5 TG mice generation and GDF5 expression profile in TG mice

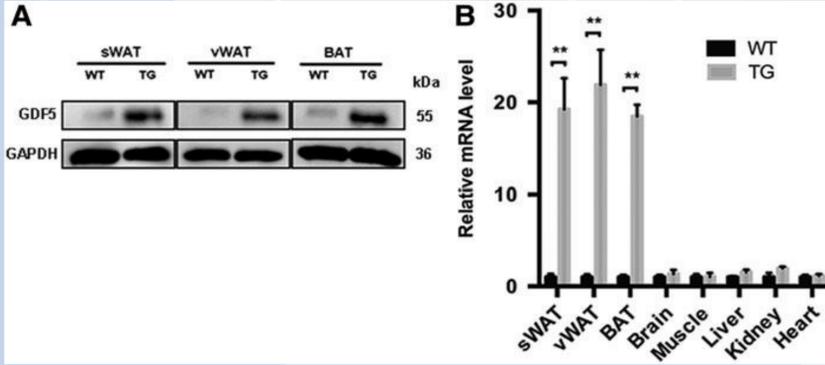


FIG. 1. Fabp4-GDF5 TG mice generation and GDF5 expression profile in TG mice. (A) Western blotting analysis of GDF5 expression levels in three adipose tissues from 7- to 8-week-old WT and TG mice. (B) qPCR data of GDF5 mRNA levels in multiple tissues from 7- to 8-week-old male littermates (n = 3).

Elevated GDF5 expression in adipose tissues increased resistance to obesity

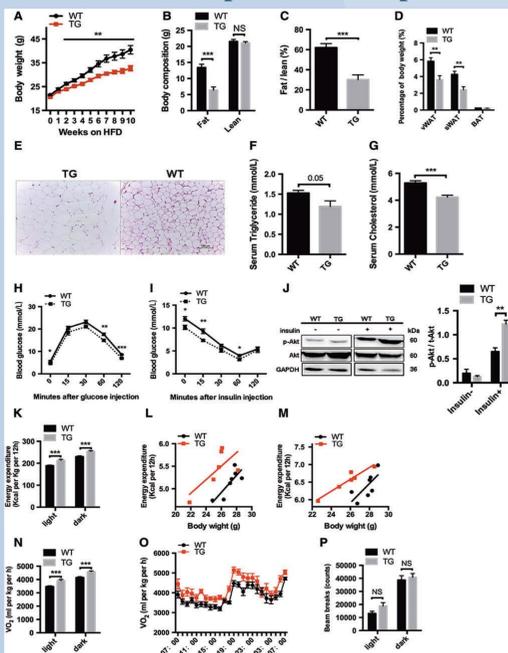


FIG. 2. (A) Growth curves of male littermates fed a HFD. HFD was started at the age of 6 weeks (n = 7–8). (B–D) Body composition (B), fat/lean mass ratio (C), and percentage of body weight of vWAT, sWAT, and BAT fat pads (D) of 16-week-old male littermates after 10 weeks of a HFD (n = 8). (E) Representative images of HE staining in sWAT sections from 16-week-old male littermates after 10 weeks of a HFD. Scale bar is 100 μ m. (F, G) Fasting serum triglycerides (n = 7) and cholesterol (n = 7) levels from 16-week-old male littermates after 10 weeks of a HFD. (H, I) Glucose levels during a glucose tolerance test (H) or an insulin tolerance test (I) of 15-week-old male littermates after 9 weeks of a HFD (n = 6). (J) Western blotting analysis of phosphorylation of Akt in sWAT from male littermates after 10 min stimulation with 5 U/kg insulin. Insulin treatment was administered to 10-week-old male littermates after 4 weeks of a HFD. (K) Energy expenditure of 9-week-old male littermates after 3 weeks of a HFD (n = 6–7). (L, M) ANCOVA of energy expenditure during the light (L) and dark (M) periods (p < 0.01; n = 6–7). (N, O) Whole-body oxygen consumption rate (VO₂) of 9-week-old male littermates after 3 weeks of a HFD, for average of the light and dark periods (N) and for a 24-h period (O) (n = 6–7). (P) Physical activity of 9-week-old male littermates after 3 weeks of a HFD for a 24-h period (n = 6–7). Results are presented as the means \pm SEM

Overexpression of GDF5 led to upregulated expression of thermogenic genes in SWAT

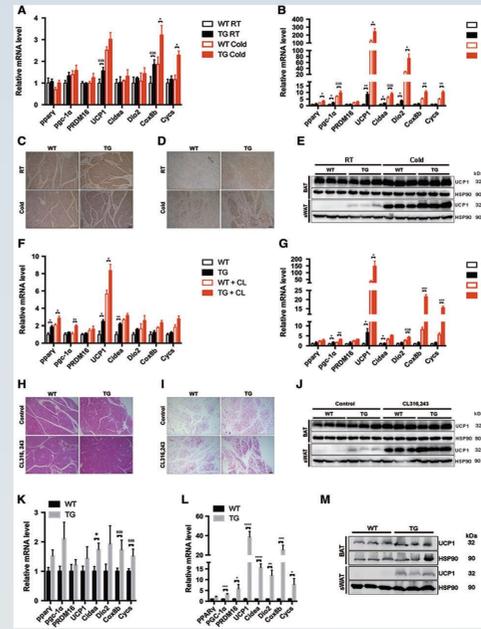


Fig.3 (A, B) Normalized gene expression of thermogenic genes in BAT (A) and sWAT (B) from male littermates at RT or after 48 h at 4C. Cold exposure was performed with 7- to 8-week-old male littermates. (C, D) Representative images of UCP1 immunostaining in BAT (C) and sWAT (D) sections from male littermates at RT or after 48 h at 4C. (E) UCP1 levels in BAT and sWAT of male littermates housed at RT or 4C for 48 h. (F, G) Normalized gene expression of thermogenic genes in BAT (F) and sWAT (G) from male littermates after five daily injections of saline or 1mg/kg CL. CL treatment was administered to 7- to 8-week-old male littermates. (H, I) HE staining in BAT (H) and sWAT (I) sections from male littermates after five daily injections of saline or 1 mg/kg CL. (J) UCP1 levels in BAT and sWAT of male littermates after five daily injections of saline or 1 mg/kg CL. (K, L) Normalized gene expression of thermogenic genes in BAT (K) and sWAT (L) of 16-week-old male littermates after 10 weeks of HFD. (M) UCP1 levels in BAT and sWAT of 16-week-old male littermates after 10 weeks of a HFD.

The P38 MAPK pathway regulated GDF5-induced thermogenesis in SWAT

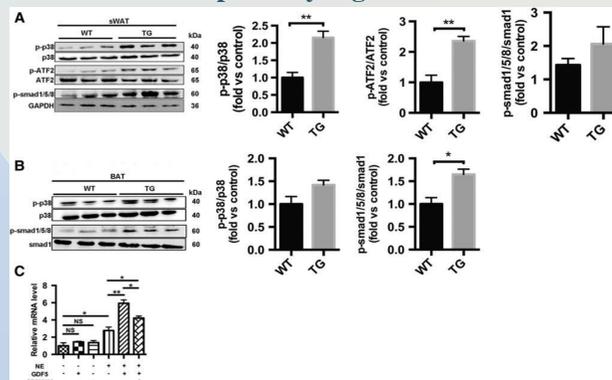


Fig.4 The P38 MAPK pathway regulated GDF5-induced thermogenesis in SWAT. (A, B) Phosphorylation of the BMP-signaling pathway in sWAT (A) and BAT (B) from 16-week-old male littermates after 10 weeks of a HFD. (C) Normalized gene expression of UCP1 from fully differentiated C3H10T1/2 cells after 4 h of stimulation with NE or not.

CONCLUSIONS

Our data suggest that GDF5 could improve insulin sensitivity and prevent metabolic syndrome, the adaptive thermogenesis in sWAT could mediate the obesity resistance effects of GDF5 in mice and partially resulted in the activation of the p38 MAPK signaling pathway.

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CONTACTS

Feihong LUO
PHONE: +86 21 64931226 EMAIL: luo_fh@163.com
ADDRESS: 399 Wanyuan Road, Minhang District, Shanghai, China

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