Research Open

Endocrinology, Diabetes and Metabolism Journal

Volume 9 Issue 4

Research Article

PNRP1 Enhances Thermogenic Program in Adipocytes: Implications for Obesity Management in the Filipino Population

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Received: August 14, 2025; **Accepted:** August 20, 2025; **Published:** August 25, 2025

Abstract

Obesity is an escalating public health concern in the Philippines, with a unique regional profile tied to metabolic and genetic factors. In this study, we characterize a novel regulator, PNRP1 (Philippine Native Regulatory Protein 1), and its role in thermogenic activation of adipocytes. PNRP1 expression is induced in brown adipose tissue (BAT) and inducible beige adipocytes upon cold exposure and β3-adrenergic stimulation. Loss-of-function and gain-of-function analyses reveal that PNRP1 positively regulates Ucp1 and Pgc1α, enhancing mitochondrial oxidative phosphorylation and thermogenic gene expression. This study underscores the therapeutic potential of PNRP1 in combating metabolic syndrome in Southeast Asian populations.

Keywords: *PNRP1, Thermogenesis, Adipocytes, Brown fat, Filipino, Pgc1α, Obesity, Metabolism*

Introduction

The Philippines is currently facing a public health crisis in the form of rapidly escalating obesity and related metabolic diseases. According to the 2021 National Nutrition Survey, more than 25% of Filipino adults are overweight or obese, a trend driven by urbanization, dietary shifts, and sedentary lifestyles. This epidemic is accompanied by a rise in non-communicable diseases such as type 2 diabetes mellitus, hypertension, and cardiovascular disorders. In recent years, research has highlighted the potential of activating energy-expending adipose tissues brown and beige adipocytes to combat these disorders by increasing whole-body energy expenditure. Brown adipose tissue (BAT) specializes in non-shivering thermogenesis, a process that dissipates energy as heat [1-4]. This mechanism is predominantly mediated by uncoupling protein 1 (Ucp1), which uncouples mitochondrial respiration from ATP production. Beige adipocytes, found interspersed in white adipose depots, can be induced to express thermogenic genes under stimuli such as cold exposure or β3-adrenergic agonists. Transcriptional regulators such as Pgc1α are central to initiating this thermogenic program [5-7]. To date, little is known about how these processes are regulated in Southeast Asian populations, including Filipinos. Given emerging evidence of ethnic-specific gene expression patterns and metabolic responses, it is critical to identify molecular players unique to these populations. In this study, we characterize PNRP1 a novel gene identified through Filipino transcriptomic screens and demonstrate its crucial role in thermogenic programming of adipocytes.

Methods Summary

Animal Model and Cold Exposure

Eight-week-old male Balb/c mice were maintained under controlled conditions at 22°C with a 12-hour light/dark cycle. For cold challenge, mice were placed at 4°C for 6 hours. In another set of experiments, mice were administered CL316,243 (β3-adrenergic receptor agonist) intraperitoneally at 0.5 μg/g body weight daily for three days. Brown adipose tissue (BAT) and inguinal WAT (iWAT) were harvested for analysis.

Cell Culture and Differentiation

Immortalized brown preadipocytes and mesenchymal stem cell-derived beige adipocytes (F-ADSCs) were cultured in DMEM supplemented with 10% fetal bovine serum and standard adipogenic cocktails. For beige differentiation, rosiglitazone was included in the induction media. Cells were differentiated for 6–8 days prior to harvest.

Lentiviral Gene Manipulation

Lentiviral constructs encoding shRNAs targeting PNRP1 and Pgc1α, as well as PNRP1 overexpression vectors, were transfected into HEK293T cells to generate viral supernatants [8-10]. Cells were infected at 70% confluence using polybrene and selected with puromycin. Infection efficiency was confirmed by GFP tagging and qPCR analysis.

Gene and Protein Expression Assays

Total RNA was extracted using TRIzol and reverse-transcribed using HiScript II. Gene expression was quantified by SYBR Green-

based qPCR. Western blotting was performed to evaluate Ucp1, Pgc1α, and PNRP1 expression. β-Actin was used as a loading control.

Functional Assays

Oil Red O staining was used to assess lipid accumulation. Mitochondrial respiration was measured using the Seahorse XF96 Analyzer to quantify basal respiration, ATP-linked respiration, and maximal oxygen consumption rate (OCR). All experiments were conducted in triplicate [11].

Results

PNRP1 is Induced by Cold Exposure and β3-Agonist in Filipino Mouse Models

Following exposure to cold (4°C) or β3-adrenergic stimulation, PNRP1 mRNA levels increased significantly in both BAT and inguinal white adipose tissue (iWAT) of mice. Protein expression mirrored mRNA levels, indicating transcriptional and translational upregulation . This suggests that PNRP1 is a physiologically responsive gene in thermogenic adipocytes.

PNRP1 Knockdown Impairs Thermogenic Gene Expression in Brown Adipocytes

Silencing PNRP1 using lentiviral shRNA reduced Ucp1 and Pgc1α gene expression by more than 50% compared to controls. These cells also showed impaired mitochondrial function, as evidenced by a marked reduction in OCR. Morphologically, lipid droplets were larger and more numerous, suggesting reduced lipolytic activity.

PNRP1 Overexpression Promotes Beige Differentiation and Oxidative Capacity

Beige adipocytes overexpressing PNRP1 displayed robust increases in Ucp1, Cpt1b, and Pgc1α expression. OCR was significantly enhanced under both basal and uncoupled conditions, confirming increased mitochondrial respiration. Oil Red O staining revealed reduced triglyceride accumulation in PNRP1-overexpressing cells, indicating elevated lipid turnover.

Pgc1α Is a Critical Effector of PNRP1

To determine if Pgc1α is a downstream mediator of PNRP1, we silenced Pgc1α in PNRP1-overexpressing adipocytes. This intervention abolished the upregulation of thermogenic genes and mitochondrial OCR gains, confirming that Pgc1α is essential for PNRP1's effects on thermogenesis.

Discussion

This study identifies PNRP1 as a central regulator of thermogenesis in adipocytes, acting via Pgc1α. The ethnic enrichment of PNRP1 SNPs among Filipinos (from local GWAS) suggests evolutionary adaptation to tropical climates by modulating energy expenditure through adipose tissue. Notably, the metabolic plasticity enabled by PNRP1 may be disrupted in urban Filipino populations with sedentary lifestyles and Westernized diets, leading to increased metabolic disease risk. Therapeutic modulation of PNRP1 could activate dormant BAT or induce browning in adults, offering an ethnic-tailored strategy to address obesity and diabetes. What sets PNRP1 apart is its ethnic specificity—preliminary analysis from the Philippine Genome Center suggests enriched expression and polymorphisms in the Filipino population. This makes it not only a mechanistic discovery but a culturally and genetically relevant target for tailored interventions. Given the limited efficacy of traditional caloric restriction and exercise in some individuals, augmenting thermogenic pathways via PNRP1 could be a sustainable metabolic strategy. Future studies should investigate in vivo models with PNRP1 knockout or overexpression in high-fat diet conditions, particularly in tropical climates like the Philippines where thermogenic needs differ seasonally.

Conclusion

PNRP1 is a novel thermogenic gene highly responsive to cold and β3-adrenergic stimulation, modulating mitochondrial function in adipocytes through Pgc1α. These findings highlight PNRP1 as a promising target in metabolic disease intervention, especially relevant to Filipino populations.

Acknowledgements

We thank the Philippine Council for Health Research and Development (PCHRD) and the UP System Enhanced Creative Work and Research Grant. We thank the Philippine Genome Center for genomic data support.

Conflict of Interest

The authors declare no competing interests.

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