Pentamethylquercetin counteracts obesity and drives brown fat-like phenotype through AMPK-mediated activation of PGC-1 alpha/FNDC5 pathway in muscle

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BACKGROUND/OBJECTIVES: To determine the effect of pentamethylquercetin (PMQ), a natural methylated quercetin derivative, on beige/brite adipocyte formation in inguinal white adipose tissue (ingWAT), and to explore its underlying mechanisms.

METHODS: Monosodium glutamate (MSG)-induced obese mice, which exhibit obesity and insulin resistance, were administered orally with PMQ at doses of 5, 10 and 20 mg/kg/d for 19 consecutive weeks. Histologic and molecular changes were examined to evaluate the browning effects of PMQ on ingWAT and the involvement of AMPK/PGC-1alpha/FNDC5 pathway was also investigated in vivo and in vitro.

RESULTS: PMQ treatment significantly improved the metabolic parameters of MSG-induced obese mice. Concomitantly, PMQ markedly induced the development of brown-like adipocytes and significantly increased UCP-1 protein level and mRNA expression of brown-fat specific genes and beige cell markers in ingWAT. Furthermore, PMQ dose-dependently upregulated the expression levels of AMPK-1alpha-FNDC5 signaling and stimulated irisin secretion in MSG mice and C2C12 myotubes. More importantly, myotube conditioned medium (MCM) after PMQ incubation generated the browning effect on 3T3-L1 cells, which could be effectively suppressed by anti-FNDC5. Meanwhile, PGC-1alpha knockdown abrogated the promoting effects of MCM incubated by PMQ on UCP-1 expression in 3T3-L1 cells. In addition, an AMPK inhibitor, compound C dramatically reduced protein levels of PGC-1alpha and FNDC5 induced by PMQ in C2C12 myotubes.

CONCLUSIONS: Our findings suggest that PMQ exerts its beiging effects on ingWAT in MSG mice, which may be attributed to activation of AMPK/PGC-1alpha/FNDC5 signaling pathway in skeletal muscle.