ABSTRACT

Obesity has progressively worsened for the past 50 years, doubling the prevalence in 1980, and estimated that 20% of the world's adult population would be obese by 2030. It is a complex, multifactorial disease of excessive fat accumulation and maladaptive adipose tissue remodelling leading to systemic metabolic decline. The hallmarks of pathological adipose tissue include blood vessel insufficiency, excessive immune cells infiltration, elevated extracellular matrix production, dysfunctional adipocytes, and chronic adipose inflammation. Conventional management strategies focusing on lifestyle interventions, physical exercise, and pharmacological management are mostly ineffective due to undesirable side effects and limited long-term efficacies. Leucine-rich alpha-2-glycoprotein 1 (LRG1) is a recently identified regulator of aberrant angiogenesis, tissue fibrosis and inflammation. Given that these pathological processes are dominant contributors to dysfunctional adipose tissue, we hypothesise that LRG1 may exert essential roles in regulating adipose tissue remodelling and systemic metabolic health. Metabolic phenotyping of *Lrg1*-null mice subjected to diet-induced obesity revealed enhanced systemic metabolic decline, including increased adiposity, increased fasting triglyceride and glycated haemoglobin A1c levels, and larger adipocyte hypertrophy and vessel density. Moreover, angiogenesis, inflammatory, and thermogenesis mRNA expressions decreased, while hypoxia and fibrosis mRNA expressions increased on LRG1-deficient mice groups. Paradoxically, while *Lrg1* transcript level was positively associated with obesity, LRG1-deficiency demonstrated significant systemic metabolic decline. These results altogether indicated a potential context-dependent role of LRG1 in metabolic homeostasis and adipose tissue remodelling.