Obesity stands out as a significant risk factor for end-stage kidney disease. Previous investigations from our group revealed that lysosomal dysfunction and impaired autophagic flux contribute to lipotoxicity in obesity-related kidney disease, observed in both human subjects and experimental animal models. However, the regulatory factors involved in mitigating renal lipotoxicity remain largely unknown. In this study, we discovered that palmitic acid strongly induced dephosphorylation and nuclear translocation of transcription factor EB (TFEB) by inhibiting the mechanistic target of rapamycin kinase complex 1 pathway. This effect occurred in a Rag GTPase–dependent manner, although it gradually diminished with extended treatment. The research then delved into the role of TFEB in the pathogenesis of obesity-related kidney disease. Mice with proximal tubular epithelial cell–specific (PTEC-specific) deficiency in Tfeb, fed a high-fat diet (HFD), exhibited increased phospholipid accumulation in enlarged lysosomes, presenting as multilamellar bodies (MLBs). Activated TFEB facilitated lysosomal exocytosis of phospholipids, aiding in the reduction of MLB accumulation in PTECs. Additionally, HFD-fed mice with PTEC-specific Tfeb deficiency displayed autophagic stagnation and worsened injury during renal ischemia/reperfusion. Finally, an association was observed between higher body mass index and increased vacuolation along with decreased nuclear TFEB in the proximal tubules of patients with chronic kidney disease. In summary, these findings highlight the critical role of TFEB-mediated lysosomal exocytosis in counteracting renal lipotoxicity, shedding light on potential therapeutic targets for obesity-related kidney disease.