The mechanistic target of rapamycin kinase complex 1 (MTORC1) is a central cellular kinase that integrates major signaling pathways, allowing for regulation of anabolic and catabolic processes including macromolecule synthesis and lysosomal biogenesis. Essential to these processes is the regulatory activity of TFEB (transcription factor EB). In a regulatory feedback loop modulating transcriptional levels of mTOR-associated GTPases, TFEB controls MTORC1 tethering to membranes and induction of anabolic processes upon nutrient replenishment. We now show that TFEB promotes expression of endocytic genes and increases rates of cellular endocytosis during homeostatic baseline and starvation conditions. TFEB-mediated endocytosis drives assembly of the MTORC1-containing nutrient sensing complex through the formation of endosomes that carry the associated proteins RRA GTPases (2), en route to lysosomes to inhibit TSC2 (via AKT-mediated phosphorylation that targets TSC2) (3), tether MTORC1 (4) and eventually promote autophagy.

TFEB-mediated endocytosis activates MTORC1 by coordinating the sorting of LYNUS components on endosomal membranes. Starvation-induced inhibition of MTORC1 promotes nuclear TFEB activity (1) that triggers expression of endocytic genes driving random formation of endosomes that shuttle LYNUS components including active p-AKT and RRA GTPases (2), en route to lysosomes to inhibit TSC2 (via AKT-mediated phosphorylation that targets TSC2) (3). Hence, TFEB-induced autophagy in the presence of MTORC1 leads to activation of MTORC1 and autophagic function.