The stress-responsive transcription factor EB (TFEB) is a master controller of lysosomal biogenesis and autophagy and plays a major role in several cancer-associated diseases. TFEB is regulated at the posttranslational level by the nutrient-sensitive kinase complex mTORC1. However, little is known about the regulation of TFEB transcription. Here, through integrative genomic approaches, we identify the immediate-early gene EGR1 as a positive transcriptional regulator of TFEB expression in human cells and demonstrate that, in the absence of EGR1, TFEB-mediated transcriptional response to starvation is impaired. Remarkably, both genetic and pharmacological inhibition of EGR1, using the MEK1/2 inhibitor Trametinib, significantly reduced the proliferation of 2D and 3D cultures of cells displaying constitutive activation of TFEB, including those from a patient with Birt-Hogg-Dubé(BHD) syndrome, a TFEB-driven inherited cancer condition. Overall, we uncover an additional layer of TFEB regulation consisting in modulating its transcription via EGR1 and propose that interfering with the EGR1-TFEB axis may represent a therapeutic strategy to counteract constitutive TFEB activation in cancer-associated conditions.