

The stress-responsive transcription factor EB (TFEB) serves as a master controller of lysosomal biogenesis and autophagy, playing a significant role in various cancer-associated diseases. While TFEB is well-known for its posttranslational regulation by the nutrient-sensitive kinase complex mTORC1, understanding its transcriptional regulation has been limited. In this study, integrative genomic approaches are employed to identify the immediate-early gene EGR1 as a positive transcriptional regulator of TFEB expression in human cells. The research demonstrates that in the absence of EGR1, the TFEB-mediated transcriptional response to starvation is impaired. Notably, both genetic and pharmacological inhibition of EGR1, achieved through the MEK1/2 inhibitor Trametinib, leads to a significant reduction in the proliferation of cells with constitutive activation of TFEB. This includes cells from a patient with Birt-Hogg-Dubé (BHD) syndrome, a TFEB-driven inherited cancer condition, cultured in both 2D and 3D environments. The findings unveil an additional layer of TFEB regulation involving the modulation of its transcription via EGR1. The study suggests that interfering with the EGR1-TFEB axis may represent a therapeutic strategy to counteract constitutive TFEB activation in cancer-associated conditions. This insight offers potential avenues for developing targeted therapeutic interventions for conditions associated with dysregulated TFEB activity.