Epithelial-mesenchymal transition (EMT) is a complex and pivotal process involved in organogenesis and is related to several pathological processes, including cancer and fibrosis. During heart development, EMT mediates the conversion of epicardial cells into vascular smooth muscle cells and cardiac interstitial fibroblasts. Here, we show that the oncogenic transcription factor EB (TFEB) is a key regulator of EMT in epicardial cells and that its genetic overexpression in mouse epicardium is lethal due to heart defects linked to impaired EMT. TFEB specifically orchestrates the EMT-promoting function of transforming growth factor (TGF) β, and this effect results from activated transcription of thymine-guanine-interacting factor (TGIF)1, a TGFβ/Smad pathway repressor. The Tgif1 promoter is activated by TFEB, and in vitro and in vivo findings demonstrate its increased expression when Tfeb is overexpressed. Furthermore, Tfeb overexpression in vitro prevents TGFβ-induced EMT, and this effect is abolished by Tgif1 silencing. Tfeb loss of function, similar to that of Tgif1, sensitizes cells to TGFβ, inducing an EMT response to low doses of TGFβ. Together, our findings reveal an unexpected function of TFEB in regulating EMT, which might provide insights into injured heart repair and control of cancer progression.