The complex and pivotal process of epithelial-mesenchymal transition (EMT) plays a crucial role in organogenesis and is associated with various pathological processes, including cancer and fibrosis. During heart development, EMT facilitates the transformation of epicardial cells into vascular smooth muscle cells and cardiac interstitial fibroblasts. In this study, we highlight the oncogenic transcription factor EB (TFEB) as a key regulator of EMT in epicardial cells, and its genetic overexpression in mouse epicardium proves lethal due to heart defects linked to impaired EMT. TFEB takes center stage in orchestrating the EMT-promoting function of transforming growth factor (TGF) β, specifically through the activation of thymine-guanine-interacting factor (TGIF)1, a repressor in the TGFβ/Smad pathway. The activation of the Tgif1 promoter by TFEB is demonstrated, with in vitro and in vivo findings confirming increased Tgif1 expression upon Tfeb overexpression. Furthermore, Tfeb overexpression in vitro hinders TGFβ-induced EMT, and this effect is nullified by silencing Tgif1. Conversely, Tfeb loss of function, akin to Tgif1 deficiency, heightens cell sensitivity to TGFβ, inducing an EMT response even at low doses of TGFβ. In summary, these findings unveil an unexpected role of TFEB in regulating EMT, offering potential insights into the repair of injured hearts and the control of cancer progression. This study sheds light on the intricate mechanisms governing EMT, which could have implications for therapeutic interventions in conditions involving EMT dysregulation.