Elucidating the signaling events that promote T-cell tolerance versus activation provides important insights for manipulating immunity in vivo. Previous studies have suggested that the absence of PKCθ results in the induction of anergy and that the balance between the induction of the transcription factors NFAT, AP1 and NF-κB plays a key role in determining whether T-cell anergy or activation is induced. Here, we examine whether Bcl-10 and specific family members of NF-κB act downstream of PKCθ to alter CD8(+)-T-cell activation and/or anergy. We showed that T cells from mice deficient in c-Rel but not NF-κB1 (p50) have increased susceptibility to the induction of anergy, similar to T cells from PKCθ-deficient mice. Surprisingly, T cells from Bcl-10-deficient mice showed a strikingly different phenotype to the PKCθ-deficient T cells, with a severe block in TCR-mediated activation. Furthermore, we have also shown that survival signals downstream of NF-κB, are uncoupled from signals that mediate T-cell anergy. These results suggest that c-Rel plays a critical role downstream of PKCθ in controlling CD8(+) T-cell anergy induction.