CD28 costimulation regulates FOXP3 in a RelA/NF-κB-dependent mechanism.

The molecular mechanisms whereby CD28 alone or associated with TCR can regulate FOXP3 expression are not understood, although the importance of CD28 as a pivotal regulator of CD4(+) CD25(+) FOXP3(+) T cells is well recognized. We previously demonstrated that unique CD28-induced, NF-κB-dependent signals were sufficient to activate FOXP3 transcription in human CD4(+) CD25(-) T cells; however, the exact mechanisms are currently unknown. In this study, we have identified novel NF-κB-binding sites on FOXP3 gene and demonstrated that CD28 signals mediated FOXP3 trans activation by nuclear translocation of RelA/NF-κB and not of c-Rel. The occupancy of FOXP3 NF-κB-binding sites by RelA dimers that correlated with histone acetylation and recruitment of Pol II were required both to initiate FOXP3 transcription and to control the promoter occupancy by NFAT. Interestingly, knockdown of RelA in CD4(+) CD25(-) T cells stimulated through TCR and CD28 significantly affected FOXP3 expression, confirming that also the transcriptional activation of FOXP3 gene by TCR in the presence of CD28-costimulatory signals is RelA-dependent. In conclusion, these data suggest a new mechanism by which FOXP3 is activated and supports the critical role of CD28 in the regulation of peripheral tolerance.