NF-KAPPAB ACTIVATION MEDIATED BY THE HTLV PROTEIN TAX REQUIRES TRAF3 FACTOR

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NF-kappaB pathway is involved in the regulation of inflammation, immune responses, development, cell survival, and proliferation. Dysregulation of NF-kappaB can lead to inflammation, autoimmune diseases and cancer. NF-kappaB transcription factors are activated in response to a range of external stimuli, including the cytokine TNF-alpha, neurotrophic factors, cell adhesion molecules, and various types of stress. Persistent activation of NF-kappaB is a prerequisite for the development of Adult T-cell Leukemia, a severe malignancy caused by Human T-cell Leukemia Virus type 1. Constitutive activation of NF-kappaB occurs in the presence of the transactivator HTLV protein Tax, required for viral gene expression and which deregulates cell host gene expression, participating to initial steps of tumorigenesis. Identifying the cellular interactors of the viral transactivator Tax contributes to dissect the cellular processes altered by viral stress. We recently reported that the TNF-receptor associated factor 3, TRAF3, a negative regulator of the non-canonical NF-kappaB pathway, forms complexes with Tax. In order to explore the functional effect on NF-kappaB activation derived by this interaction, we developed a TRAF3-deficient cell line using the CRISPR/Cas9 genome editing system. We found that TRAF3-deficient cells showed a basal activation of NF-kappaB promoter, a partial nuclear localization of the transcriptional factor p65 and the processing of the p100 protein, confirming the negative role of TRAF3 in modulating NF-kappaB activation. Applying the TRAF3-KO cell model, we showed that Tax-mediated NF-kappaB activation was impaired in TRAF3-deficient cells. Furthermore, we demonstrated that TRAF3 was recruited in cytoplasmic complexes containing Tax and the antisense protein APH-2. These results contribute to untangling the mechanism of NF-kappaB deregulation mediated by retroviral proteins such as Tax, highlighting a novel role of TRAF3 factor in response to viral stimuli.