TNF-alpha-dependent loss of IKKbeta-deficient myeloid progenitors triggers a cytokine loop culminating in granulocytosis.

Loss of I?B kinase (IKK) ?-dependent NF-?B signaling in hematopoietic cells is associated with increased granulopoiesis. Here we identify a regulatory cytokine loop that causes neutrophilia in Ikk?-deficient mice. TNF?-dependent apoptosis of myeloid progenitor cells leads to the release of IL-1?, which promotes Th17 polarization of peripheral CD4(+) T cells. Although the elevation of IL-17 and the consecutive induction of granulocyte colony-stimulating factor compensate for the loss of myeloid progenitor cells, the facilitated induction of Th17 cells renders Ikk?-deficient animals more susceptible to the development of experimental autoimmune encephalitis. These results unravel so far unanticipated direct and indirect functions for IKK? in myeloid progenitor survival and maintenance of innate and Th17 immunity and raise concerns about long-term IKK? inhibition in IL-17-mediated diseases.