To explore the functional significance of cGMP-dependent protein kinase type I (cGKI) in the regulation of erythrocyte survival, gene-targeted mice lacking cGKI were compared with their control littermates. By the age of 10 weeks, cGKI-deficient mice exhibited pronounced anemia and splenomegaly. Compared with control mice, the cGKI mutants had significantly lower red blood cell count, packed cell volume, and hemoglobin concentration. Anemia was associated with a higher reticulocyte number and an increase of plasma erythropoietin concentration. The spleens of cGKI mutant mice were massively enlarged and contained a higher fraction of Ter119(+) erythroid cells, whereas the relative proportion of leukocyte subpopulations was not changed. The Ter119(+) cGKI-deficient splenocytes showed a marked increase in annexin V binding, pointing to phosphatidylserine (PS) exposure at the outer membrane leaflet, a hallmark of suicidal erythrocyte death or eryptosis. Compared with control erythrocytes, cGKI-deficient erythrocytes exhibited in vitro a higher cytosolic Ca(2+) concentration, a known trigger of eryptosis, and showed increased PS exposure, which was paralleled by a faster clearance in vivo. Together, these results identify a role of cGKI as mediator of erythrocyte survival and extend the emerging concept that cGMP/cGKI signaling has an
antiapoptotic/prosurvival function in a number of cell types in vivo.