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Titel des Beitrags: Thrombocytosis as a response to high interleukin-6 levels in cGMP-dependent protein kinase I mutant mice.

Abstract: The purpose of this study was to investigate the influence of cGMP-dependent kinase I (cGKI) on platelet production. We used hematology analyser to measure platelet counts in conventional cGKI-null mutants (cGKI(L1/L1)), gene-targeted cGKI/?/? rescue mice (referred to as cGKI-smooth muscle [SM]) in which cGKI expression is specifically restored only in SM, platelet factor 4-Cre(tg/+); cGKI(L2/L2) mice in which the cGKI protein was specifically deleted in the megakaryocyte/platelet lineage and cGKI-deficient bone marrow-chimeras. Thrombocytosis was detected in cGKI(L1/L1) and in cGKI-SM. In contrast, neither platelet factor 4-Cre(tg/+); cGKI(L2/L2) nor cGKI-deficient bone marrow-chimeras displayed a thrombocytosis phenotype, indicating that the high platelet count in cGKI(L1/L1) and cGKI-SM mutants is attributable to loss of an extrinsic signal rather than reflecting an intrinsic defect in megakaryopoiesis. Cytometric analyses further showed that stimulation of bone marrow-derived wild-type megakaryocytes in vitro using serum preparations obtained from cGKI-SM mutants strongly accelerated megakaryopoiesis, suggesting that the high platelet count develops in response to serum factors. Indeed, using ELISA assay,
we found elevated levels of interleukin-6, a known stimulator of thrombopoiesis, in cGKI-SM mutant serum, whereas interleukin-6 levels were unaltered in platelet factor 4-Cre(+/+); cGKI(L2/L2) mice and cGKI-deficient bone marrow-chimeras. Accordingly, antibody-mediated blockade of interleukin-6 normalized platelet counts in cGKI-SM mice. Abnormal cGMP/cGKI signaling in nonhematopoietic cells affects thrombopoiesis via elevated interleukin-6 production and results in thrombocytosis in vivo. Dysfunction of cGMP/cGKI signaling in nonhematopoietic cells contributes to a high platelet count, which is potentially associated with thrombosis.