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Anti-interleukin-6 therapy for treatment of high platelet counts in cGMP-dependent protein kinase I gene-targeted mice

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Background

The cyclic guanosine-3',5'-monophosphate (cGMP)/cGMP-dependent protein kinase type I (cGKI) pathway is a potent negative regulator of platelet adhesion and aggregation [1]; however, the role of cGMP/cGKI for platelet biogenesis *in vivo* is unclear.

Results

Here we report thrombocytosis in conventional cGKI null mutants ($cGKI^{L1/L1}$) and gene-targeted cGKIα/β rescue mice (referred to as cGKI-SM) with cGKI expression specifically restored in smooth muscle (SM), but not in other cell types [2-4]. In contrast, conditional knockouts lacking the cGKI protein specifically in the megakaryocyte (MK)/platelet lineage ($Pf4\text{-}Cre^{tg/+}$; $cGKI^{L2/L2}$) did not display a related thrombocytosis phenotype, indicating that the high platelet count of $cGKI^{L1/L1}$ and cGKI-SM mutants is rather a reactive response than an intrinsic defect in megakaryopoiesis. In line with these findings, wild-type (WT) mice engrafted with cGKI-deficient bone-marrow (BM) cells showed full reconstitution of haematopoiesis and normal platelet counts upon myeloablative radiotherapy. Stimulation of BM-derived WT MKs using serum preparations from cGKI-SM mutants strongly accelerated megakaryopoiesis, suggesting that their high platelet counts develop in response to soluble factors. Indeed, we confirm elevated Interleukin-6 (IL-6) serum levels [5,6], a known cause for reactive thrombocytosis, in cGKI-SM mutants, whereas IL-6 was unaltered in $Pf4\text{-}Cre^{tg/+}$; $cGKI^{L2/L2}$ mice and cGKI-deficient BM chimaeras. Vice versa, antibody-mediated blockage of IL-6 reduced platelet counts in cGKI-SM mice, but not in WT mice.

Conclusion

We conclude that abnormal signalling of cGMP/cGKI in non-hematopoietic cells affects thrombopoiesis via IL-6 resulting in a reactive thrombocytosis *in vivo*.

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