Wild-type Kras expands and exhausts hematopoietic stem cells.

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Public Summary:
The protein, KRas, has an essential role in regulating cellular survival, proliferation and differentiation. Mutations in KRas cause blood system cancers in mice, but little is known about the effects of increased expression of normal KRas protein. We evaluated the blood system and blood stem cell content of mice that were engineered to have increased expression of normal KRas. We discovered that increased KRas protein promoted blood stem cell self-renewal and proliferation that was demonstrated when the stem cells were transplanted into recipient mice. However, after the stress of a second transplantation, the stem cells that overexpressed KRas were exhausted and lost their stem cell function. Finally, when mice were stressed with radiation exposure, the animals that had increased KRas protein displayed more rapid recovery of the blood system after injury compared to control mice. In summary, this study demonstrated that KRas protein strongly promotes blood stem cell growth and self-renewal, but at the expense of early exhaustion.

Scientific Abstract:
Oncogenic Kras expression specifically in hematopoietic stem cells (HSCs) induces a rapidly fatal myeloproliferative neoplasm in mice, suggesting that Kras signaling plays a dominant role in normal hematopoiesis. However, such a conclusion is based on expression of an oncogenic version of Kras. Hence, we sought to determine the effect of simply increasing the amount of endogenous wild-type Kras on HSC fate. To this end, we utilized a codon-optimized version of the murine Kras gene (Krasex3op) that we developed, in which silent mutations in exon 3 render the encoded mRNA more efficiently translated, leading to increased protein expression without disruption to the normal gene architecture. We found that Kras protein levels were significantly increased in bone marrow (BM) HSCs in Krasex3op/ex3op mice, demonstrating that the translation of Kras in HSCs is normally constrained by rare codons. Krasex3op/ex3op mice displayed expansion of BM HSCs, progenitor cells, and B lymphocytes, but no evidence of myeloproliferative disease or leukemia in mice followed for 12 months. BM HSCs from Krasex3op/ex3op mice demonstrated increased multilineage repopulating capacity in primary competitive transplantation assays, but secondary competitive transplants revealed exhaustion of long-term HSCs. Following total body irradiation, Krasex3op/ex3op mice displayed accelerated hematologic recovery and increased survival. Mechanistically, HSCs from Krasex3op/ex3op mice demonstrated increased proliferation at baseline, with a corresponding increase in Erk1/2 phosphorylation and cyclin-dependent kinase 4 and 6 (Cdk4/6) activation. Furthermore, both the enhanced colony-forming capacity and in vivo repopulating capacity of HSCs from Krasex3op/ex3op mice were dependent on Cdk4/6 activation. Finally, BM transplantation studies revealed that augmented Kras expression produced expansion of HSCs, progenitor cells, and B cells in a hematopoietic cell-autonomous manner, independent from effects on the BM microenvironment. This study provides fundamental demonstration of codon usage in a mammal having a biological consequence, which may speak to the importance of codon usage in mammalian biology.