The Centre for Blood Research Seminar Series

CBR

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Wednesday, June 19th, 2013

LSC 3 - Life Sciences Centre
2350 Health Sciences Mall

12-1pm

"miR-146a Regulates Hematopoietic Stem Cell Maintenance and Cell Cycle Entry"

Maintenance of blood homeostasis depends on the balance between self-renewal of hematopoietic stem cells (HSCs) and their differentiation into blood cell progenitors. A variety of different intrinsic or extrinsic regulators, including multiple microRNA (miRNA) species, have been described to play a role in the regulation of these processes. Disruption of any of these regulators could lead to stem cell exhaustion or increased risk of leukemogenesis. Given recent reports of the role of miR-146a in malignant hematopoiesis, we evaluated its role in hematopoietic stem progenitor cell (HSPC) function. We show that miR-146a is highly expressed in HSCs and its expression decreases in committed progenitors. miR-146a- deficient HSCs had dramatically reduced self-renewal capacity as measured by serial competitive bone marrow transplantation assays. The lower self-renewal capacity was accompanied by decreased quiescence in miR-146a-/- HSPCs (Lin- Sca-1+ c-kit-, LSK) and their increased proliferation. We further showed that increased proliferation of HSPCs is cell intrinsic. By sorting EPCR+ CD48- CD150+ (ESLAM) HSCs and examining cell division kinetics at the single cell level, we found that miR -146a-/- HSC undergo cell division earlier and differentiate more rapidly than wild-type HSCs, thereby producing larger colonies containing more differentiated (Lin+) cells. Our data provide evidence that miR-146a loss attenuates HSC quiescence and impairs their self-renewal ability, leading to hyperproliferation of progenitor cells. The phenotype seen is cell autonomous and the findings suggest that miR-146a plays a critical role in maintaining long term HSC function.

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