Genomic imprinting maintains a reserve pool of blood-forming stem cells in mouse bone marrow

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Hematopoietic stem cells—bone marrow-derived adult stem cells that give rise to the wide variety of specialized blood cells—come in two flavors: the reserve force sits quietly waiting to be called upon while the active arm continually proliferates spawning billions of blood cells every day. In their latest study, researchers at the Stowers Institute for Medical Research reveal a new mechanism that is critical in maintaining the delicate balance between the two.

Publishing in the July 17 advance online issue of *Nature*, the team led by Stowers Investigator Linheng Li, Ph.D., reports that genomic imprinting, a process that specifically shuts down one of the two gene copies found in each mammalian cell, prevents the reservists from being called up prematurely.

"Active HSCs (hematopoietic stem cells) form the daily supply line that continually replenishes worn-out blood and immune cells while the reserve pool serves as a backup system that replaces damaged active HSCs and steps in during times of increased need," explains Li. "In order to maintain a long-term strategic reserve of hematopoietic stem cells that lasts a lifetime it is very important to ensure that the back-up crew isn't mobilized all at once. Genomic imprinting provides an additional layer of regulation that does just that."

Sexual reproduction yields progeny with two copies, or alleles, for each

gene, one from the mother and one from the father. Most genes are expressed from both copies but in mammals and marsupials a small subset of genes receives a mark, or "imprint" during the development of egg or sperm cells. These genomic imprints not only differentiate between genes of maternal and paternal origin and but specifically shut down one copy of those genes in the offspring.

Genomic imprinting is an important mechanism for regulating fetal growth and development and, not surprisingly, faulty imprinting has been linked to human disease. But whether imprinting also plays a role in adult stem cells had remained elusive.

Earlier mouse studies by Li and his collaborators had indicated that the expression of several imprinted genes changes as hematopoietic stem cells embark on their journey from quiescent reserve cells to multi-lineage progenitor cells, which form the many highly specialized cell types that circulate within the blood stream.

For the current study, the Stowers researchers focused on a differentially imprinted control region, which drives the reciprocal expression of H19 from the maternal allele and Igf2 (Insulin growth factor 2) from the paternal allele.

The study's first author Aparna Venkatraman, Ph.D., formerly a postdoc in the Li Lab and now an independent investigator at the Centre for Stem Cell Research at the Christian Medical College in Vellore, India, developed a mouse model that allowed her to specifically excise the imprinting control region from the maternal allele. As a result, the H19 gene, which restricts growth, was no longer active while the Igf2 gene, which promotes cell division, was now expressed from both the paternal and the maternal allele.

To gauge the effect off the loss of imprinting control on the maintenance

of the quiescent hematopoietic stem cell pool, Venkatraman analyzed the numbers of quiescent, active and differentiated hematopoietic stem cells in mouse bone marrow.

"A large number of quiescent hematopoietic stem cells was activated simultaneously when the epigenetic control provided by genomic imprinting was removed," explains Venkatraman. "It created a wave of activated stem cells that moved through the different maturation stages."

She then followed up with a closer look at role of the Igf2 signaling pathway in coaxing quiescent hematopoietic stem cells to start dividing and maturing into multi-lineage progenitors that ultimately give rise to specialized blood cells.

Igf2, an important growth factor, is highly active during fetal development and its misregulation leads to overgrowth disorders such as Beckwith-Wiedemann Syndrome. It exerts its growth promoting effects through the Igf1 receptor, which induces an intracellular signaling cascade that stimulates cell proliferation.

The expression of the Igf1 receptor itself is regulated by H19. The H19 gene is unusual in that it encodes a regulatory microRNA, known as miR-675, which in turn suppresses translation of the Igf1 receptor. "When the imprinting block is lifted, the Igf2-Igf1r signaling pathway is activated," said Venkatraman. "The resulting growth signal triggers the inappropriate activation and proliferation of quiescent HSCs, which eventually leads to the premature exhaustion of the reserve pool."

The roundworm *Caenorhabditis elegans* provided the first clues that diminished insulin/IGF signaling can increase lifespan and delay aging. "Here the IGF pathway is conserved but subject to imprinting, which inhibits its activity in quiescent reserve stem cells," says Li. "This ensures the long-term maintenance of the blood system, which in turn is

supports the longevity of the host."

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