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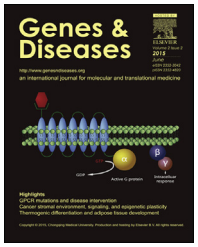

VIEWS ON NEWS

CXCR4 haploinsufficiency: An unconventional twist toward better bone marrow engraftment?

One of the major obstacles limiting the success of hematopoietic reconstitution appears to be the low efficiency of hematopoietic stem cell (HSC) engraftment in the recipient's bone marrow. Among the key factors regulating the hematopoietic reconstitution, the stromal-derived factor-1 (SDF-1)/chemokine receptor CXCR4 axis has long been known to be crucial due to its roles in HSC functions, such as homing/mobilization, engraftment, and quiescence. The SDF-1/CXCR4-mediated marrow engraftment processes have been mostly dissected through loss of function experiments involving SDF-1/CXCR4 signals.[1] There have been no previously published reports indicating whether manipulation of the SDF-1/CXCR4 axis can lead to enhanced HSC engraftment in a competitive transplantation model using syngeneic mice. However, this notion is about to change in view of a recent discovery by a group of scientists from the NIH and several prominent universities.[2] While studying one of the first reported cases of spontaneous remission of WHIM syndrome, a primary immunodeficiency disease caused by autosomal dominant gain-of-function CXCR4 mutations, this group of scientists, led by Dr. Philip Murphy, observed that the deletion of the mutant CXCR4 disease allele, together with another 163 genes from one copy of chromosome 2 in marrow HSC/progenitors, led to durable myeloid reconstitution of the patient's bone marrow. The authors then demonstrated in an analogous murine model that the loss of a CXCR4 WHIM allele in mouse bone marrow conferred enhanced engraftment compared with disease allele-bearing murine bone marrow cells, thus confirming that deletion of the mutant CXCR4 gene alone may have been sufficient to sustain the HSC marrow engraftment and correct the WHIM phenotype in the studied case. Further, the authors demonstrated that hemizygous CXCR4 bone marrow cells also have a competitive advantage over wild type cells in mice. This serendipitous discovery is certain to add a new twist to the paradigm of the SDF-1/CXCR4 axis, while raising the prospect of partial inactivation of CXCR4 as a novel strategy to improve the outcomes of HSC transplantation.

Conflicts of interest

The author has no conflict of interest to declare.

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