Therefore, in a world in which the HSC state can be programmed from adult progenitor cells, why should we care about HSC formation in the embryo? The answer to this question is beautifully illustrated by experiments performed by Mascarenhas et al using the JAKV617F expression model. JAKV617F is an acquired mutation that occurs within the human population, producing a constitutively active Jak2 that drives the formation of myeloproliferative neoplasms (MPNs). The JAKV617F mouse model used in this study, which expresses JAKV617F under the regulatory control of the endogenous Jak2 locus, results in the onset of erythrocytosis and thrombocytosis within a number of weeks and can be effectively transferred via bone marrow transplantation. Mascarenhas et al found that if HSCs from the E11.5 AGM region were used as donor material, the expected pathology did not develop (no evidence of erythrocytosis or thrombocytosis was detected over a prolonged period of time and across 2 rounds of transplantation) and the DNA damage that characterizes adult JAKV617F cells was absent. From these data, the authors concluded that even when exposed to the adult environment, HSCs of embryonic origin and their progeny remained resistant to the potent effects of JAKV617F, implying that some degree of imprinting occurred.

Although it remains unclear how the level of JAKV617F expression from embryonic HSC grafts compares with those of HSCs from adult bone marrow origin, this is an exciting observation with regard to the application of developmental hematopoiesis to personalized therapeutic translation (such as the induction of the HSC state from pluripotent cells or the direct reprogramming of adult material into HSCs): if embryonic-like HSCs can be generated in vitro, any of the unknown factors that predispose an individual to the JAKV617F mutation could be neutralized.

One critical question is why does JAKV617F not result in MPN development following embryonic HSC transplantation? Mascarenhas et al suggest one possible explanation: that higher levels of Snca3 (an effective suppressor of both wild-type and mutant Jak2) expression in the embryonic tissue effectively manages this genetic lesion. Although testing of this hypothesis will undoubtedly follow, this study highlights a facet of embryonic HSC transplantation into the adult environment that we are yet to understand: to what extent does the adult bone marrow niche alter the genomic landscape of the donor HSC? For the SOCS3-JAKV617F axis to hold true, one would predict that the embryonic donor HSC graft, including downstream progeny, would retain the higher level of SOCS3 expression. Understanding this and the broader changes (or lack thereof) that occur following engraftment of the embryonic HSC on the adult environment is surely the next critical step.

It will be fascinating to see which other pathways induced by genetic lesions can be bypassed by using adult-like HSCs from the embryonic organism.

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Comment on Man et al, page 2322

Context matters in MLL-AF9–driven leukemias

Christopher Y. Park MEMORIAL SLOAN-KETTERING CANCER CENTER

In this issue of Blood, Man et al demonstrate that the transforming activity of the leukemic fusion oncogene MLL-AF9 is regulated by inhibitor of DNA binding 1 (Id1), a dominant-negative regulator of E protein transcription factors. Although Id1 is not required for MLL-AF9–induced transformation, Id1 exerts a cell context–specific effect on this process, as loss of Id1 inhibits the development of MLL-AF9 leukemias initiated from fetal liver (FL) hematopoietic stem/progenitor cells (HSPCs), but enhances this process when leukemia is initiated from adult bone marrow HSPCs. The results from the adult HSPCs were particularly surprising because previous studies showed that Id1 is required to maintain adult hematopoietic stem cell (HSC) self-renewal and their undifferentiated state. Despite these cell-of-origin–specific effects of Id1, deletion of the Id1 target gene p21 was sufficient to rescue Id1-dependent phenotypes in leukemias initiated from both FL and adult HSPCs.

To further investigate the mechanisms by which Id1 exerts its effects on leukemogenesis, the authors measured Id1 expression and showed that FL HSPCs express higher levels of Id1 mRNA than adult HSPCs (see figure). This finding suggests that FL HSPCs may be more dependent on Id1 for their self-renewal properties than adult HSCs and that loss of Id1 reduces their susceptibility to transformation and/or the
Fetal liver and adult mouse HSPCs exhibit different dependencies on Id1 for MLL-AF9-mediated leukemogenesis. Retroviral transduction of fetal liver HSPCs and adult bone marrow with MLL-AF9 induces acute myeloid leukemia (AML); however, deletion of Id1 in fetal liver HSPCs significantly attenuates leukemogenesis, whereas deletion of Id1 in adult bone marrow HSPCs promotes leukemic development. Despite these differences, in both cell contexts, p21, a target of Id1, mediates these effects.

**REFERENCES**


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Christopher Y. Park