

Young endothelial cells revive aging blood

Vivian Y. Chang,¹ Christina M. Termini,² and John P. Chute^{2,3,4}

¹Division of Hematology/Oncology, Department of Pediatrics, ²Division of Hematology/Oncology, Department of Medicine, ³Eli and Edythe Broad Center for Stem Cell Research, and ⁴Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, California, USA.

The hematopoietic system declines with age, resulting in decreased hematopoietic stem cell (HSC) self-renewal capacity, myeloid skewing, and immune cell depletion. Aging of the hematopoietic system is associated with an increased incidence of myeloid malignancies and a decline in adaptive immunity. Therefore, strategies to rejuvenate the hematopoietic system have important clinical implications. In this issue of the *JCI*, Poulos and colleagues demonstrate that infusions of bone marrow (BM) endothelial cells (ECs) from young mice promoted HSC self-renewal and restored immune cell content in aged mice. Additionally, delivery of young BM ECs along with HSCs following total body irradiation improved HSC engraftment and enhanced survival. These results suggest an important role for BM endothelial cells (ECs) in regulating hematopoietic aging and support further research to identify the rejuvenating factors elaborated by BM ECs that restore HSC function and the immune repertoire in aged mice.

Aging and the decline of hematologic function

The population of the United States is inexorably aging. By 2030, between 20% and 25% of Americans will be over the age of 65 (1). Commensurate with the aging process, degenerative diseases occur with increased frequency, afflicting the neurologic, cardiovascular, and hematologic systems (2). Regenerative medicine is based on the premise that delivery of young or pluripotent stem cells can rejuvenate degenerated or exhausted organ systems. In support of this hypothesis, Castellano et al. recently demonstrated that infusions of cord blood plasma proteins revitalized the hippocampus and improved cognitive function in aged mice (3).

Aging in the hematopoietic system is characterized by hematopoietic stem cell (HSC) exhaustion, immune function decline, myeloid skewing, and an increased incidence of myelodysplasia, myeloproliferative diseases, and leukemia (4, 5). While allogeneic hematopoi-

etic cell transplantation can cure a subset of patients with hematologic malignancies, targeted restoration of the aged bone marrow (BM) microenvironment or “niche” has not been demonstrated. As HSC self-renewal depends on paracrine signals from both the BM vascular and perivascular niches, strategies to revitalize the aging vascular niche could potentially reanimate hematopoietic system function during aging (6–9). In this issue, Poulos et al. demonstrate that infusions of young BM endothelial cells (ECs) rejuvenate the aged hematopoietic system in murine models (10).

Young BM ECs support HSC function

Poulos and colleagues demonstrate a decline in BM EC numbers, increased BM vascular leakiness, and elevated intracellular ROS levels in ECs from aged (24-month-old) C57BL/6 mice compared with those from young (3-month-old) mice. Furthermore, aged BM ECs displayed decreased prolifera-

tive and angiogenic potential and decreased expression of paracrine factors, including stem cell factor, CXCL12, and Jagged1, which are integral to the HSC-supportive function of BM ECs (6–9). Utilizing an ex vivo model to test the hematopoietic-instructive function of BM ECs, Poulos et al. showed that coculture of young BM progenitor cells with aged BM ECs caused a decline in the HSC-repopulating capacity, while coculture of aged BM progenitor cells with young ECs rescued the HSC-repopulating capacity, albeit incompletely.

In a series of in vivo experiments, Poulos and colleagues demonstrated that serial infusions of aged BM ECs failed to rescue HSC content in young mice following high-dose total body irradiation, whereas identical infusions of young ECs into young, irradiated mice strongly promoted both hematologic recovery and HSC regeneration. In a complementary study, infusion of young ECs also promoted hematologic recovery in irradiated, aged mice, while also catalyzing the regeneration of HSCs with in vivo repopulating capacity (Figure 1). Of note, while young EC infusions did not correct the myeloid skewing inherent to the aged HSC population, B and T lymphoid reconstitution was increased following young EC infusions. In a model of suboptimal BM transplantation, infusion of young ECs augmented hematopoietic recovery and HSC reconstitution in mice; the latter result suggests that coinfusion of autologous ECs could have therapeutic potential in patients who collect suboptimal autologous grafts for transplantation. Mechanistically, coinfusion of young ECs decreased radiation-mediated damage to the BM vasculature, suggesting that EC infusions promote hematopoietic regeneration, in part, via mitigation of radiation damage to the BM vascular niche.

Conclusions

Together, these observations by Poulos et al. (10) suggest that cellular therapy with young ECs can, in principle, revive

► Related Article: p. 4163

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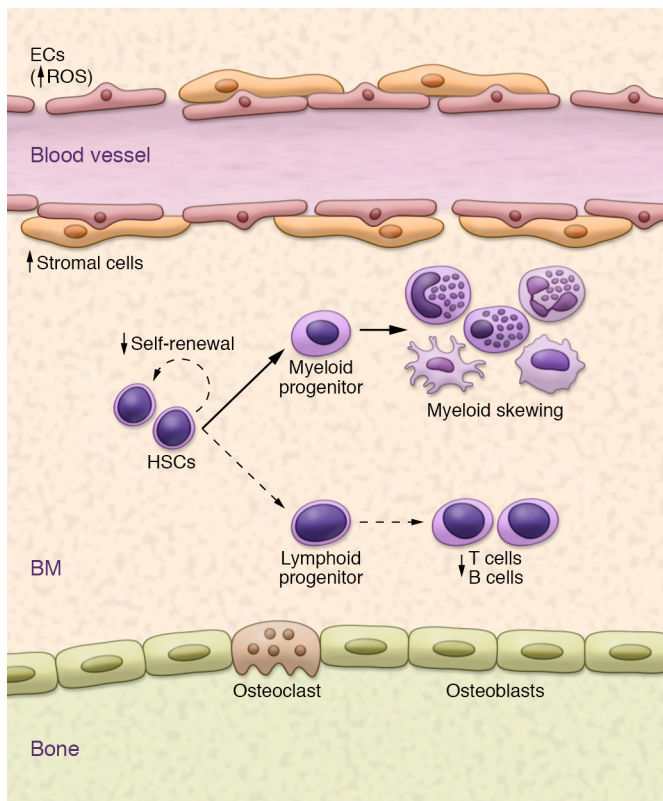
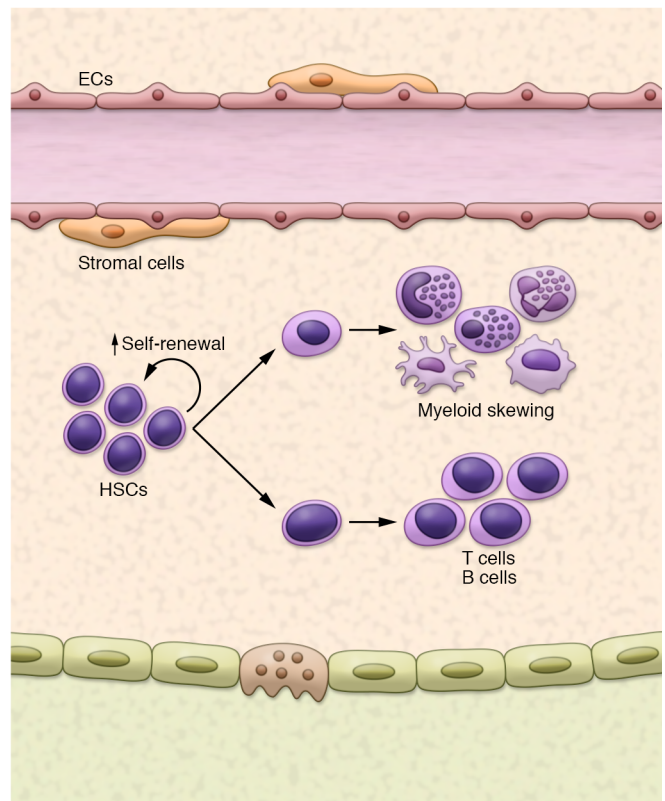
A Aged, irradiated mice**B** Aged, irradiated mice + young ECs

Figure 1. Infusion of BM ECs from young mice rejuvenates HSCs in aged, irradiated mice. In aged mice, there is a decline in the number of BM ECs, increased leakiness of the BM vasculature, and elevated intracellular ROS levels. The aged hematopoietic system is characterized by reduced HSC regenerative capacity, loss of T and B lymphocytes, and myeloid skewing. In this issue, Poulos and colleagues show that infusion of young ECs into aged, irradiated mice improves age-associated defects in BM ECs, restores HSC self-renewal capacity, and increases B and T cell numbers.

an aged HSC pool and hematopoietic system. These studies also highlight the translational potential of infusions of (young) ECs to accelerate hematopoietic recovery in clinically relevant scenarios. As prior studies by Poulos et al. (11) and others (12) have shown that infused ECs do not engraft in the BM vasculature, this implies that young ECs secrete soluble factors that act either directly on aged HSCs or indirectly on aged niche cells to rejuvenate the hematopoietic system. Identification of these EC-derived “fountains of youth” represents the next great challenge in understanding this process and may lead to restorative therapies that do not require cell infusion.

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Address correspondence to: John P. Chute, Division of Hematology/Oncology, Eli and Edythe Broad Center for Stem Cell Research, Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, California 90095, USA. Phone: 310.206.3037; Email: jchute@mednet.ucla.edu.

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