

- (2003). Osteoblastic cells regulate the hematopoietic stem cell niche. *Nature* 425:841–846.
2. Zhang J, C Niu, L Ye, H Huang, X He, WG Tong, J Ross, J Haug, T Johnson, et al. (2003). Identification of the hematopoietic stem cell niche and control of the niche size. *Nature* 425:836–841.
3. Arai F, A Hirao, M Ohnura, H Sato, S Matsukawa, K Takubo, K Ito, GY Koh and T Suda. (2004). Tie2/angiopoietin-1 signaling regulates hematopoietic stem cell quiescence in the bone marrow niche. *Cell* 118:149–161.
4. Mendez-Ferrer S, TV Michurina, F Ferraro, A Mazloof, BD Macarthur, SA Lira, DT Scadden, A Ma'ayan, GN Enikolopov and PS Frenette. (2010). Mesenchymal and hematopoietic stem cells form a unique bone marrow niche. *Nature* 466:829–834.
5. Omatsu Y, T Sugiyama, H Kohara, G Kondoh, N Fujii, K Kohno and T Nagasawa. (2010). The essential functions of adipose-osteogenic progenitors on the hematopoietic stem and progenitor cell niche. *Immunity* 33:387–399.
6. Ding L, TL Saunders, G Enikolopov and SJ Morrison. (2012). Endothelial and perivascular cells maintain hematopoietic stem cells. *Nature* 481:457–462.
7. Ding L and SJ Morrison. (2013). Hematopoietic stem cells and early lymphoid progenitors occupy distinct bone marrow niches. *Nature* 495:231–235.
8. Greenbaum A, YM Hsu, RB Day, LG Schuettpelz, MJ Christopher, JN Borgerding, T Nagasawa and DC Link. (2013). CXCL12 in early mesenchymal progenitors is required for hematopoietic stem-cell maintenance. *Nature* 495:227–230.
9. Mendez-Ferrer S, D Lucas, M Battista and PS Frenette. (2008). Hematopoietic stem cell release is regulated by circadian oscillations. *Nature* 452:442–447.
10. Christopher MJ, F Liu, MJ Hilton, F Long and DC Link. (2009). Suppression of CXCL12 production by bone marrow osteoblasts is a common and critical pathway for cytokine-induced mobilization. *Blood* 114:1531–1539.
11. Carmeliet P, V Ferreira, G Buerer, S Pollefeys, L Kieckens, M Gertsenstein, M Fahrig, A Vandenhoeck, K Harpal, et al. (1996). Abnormal blood vessel development and lethality in embryos lacking a single VEGF allele. *Nature* 380:435–439.
12. Ferrara N, K Carver-Moore, H Chen, M Dowd, L Lu, KS O'Shea, L Powell-Braxton, KJ Hillan and MW Moore. (1996). Heterozygous embryonic lethality induced by targeted inactivation of the VEGF gene. *Nature* 380:439–442.
13. Gerber HP, AK Malik, GP Solar, D Sherman, XH Liang, G Meng, K Hong, JC Marsters and N Ferrara. (2002). VEGF regulates hematopoietic stem cell survival by an internal autocrine loop mechanism. *Nature* 417:954–958.
14. Chan CK, CC Chen, CA Luppen, JB Kim, AT DeBoer, K Wei, JA Helms, CJ Kuo, DL Kraft and IL Weissman. (2009). Endochondral ossification is required for hematopoietic stem-cell niche formation. *Nature* 457:490–494.
15. Hattori K, S Dias, B Heissig, NR Hackett, D Lyden, M Tatevo, DJ Hiecklin, Z Zhu, L Witte, et al. (2001). Vascular endothelial growth factor and angiopoietin-1 stimulate postnatal hematopoiesis by recruitment of vasculogenic and hematopoietic stem cells. *J Exp Med* 193:1005–1014.
16. Mizuguchi H and MA Kay. (1998). Efficient construction of a recombinant adenovirus vector by an improved *in vitro* ligation method. *Hum Gene Ther* 9:2577–2583.
17. Mizuguchi H and MA Kay. (1999). A simple method for constructing E1- and E1/E4-deleted recombinant adenoviral vectors. *Hum Gene Ther* 10:2013–2017.
18. Xu ZL, H Mizuguchi, A Ishii-Watabe, E Uchida, T Mayumi and T Hayakawa. (2001). Optimization of transcriptional regulatory elements for constructing plasmid vectors. *Gene* 272:149–156.
19. Sakurai H, K Tashiro, K Kawabata, T Yamaguchi, F Sakurai, S Nakagawa, H Mizuguchi. (2008). Adenoviral expression of suppressor of cytokine signaling-1 reduces adenovirus vector-induced innate immune responses. *J Immunol* 180:4931–4938.
20. Koizumi N, H Mizuguchi, N Utoguchi, Y Watanabe and T Hayakawa. (2003). Generation of fiber-modified adenovirus vectors containing heterologous peptides in both the HI loop and C terminus of the fiber knob. *J Gene Med* 5:267–276.
21. Nakamura Y, F Arai, H Iwasaki, K Hosokawa, K Kobayashi, Y Gomei, Y Matsumoto, H Yoshihara and T Suda. (2010). Isolation and characterization of endosteal niche cell populations that regulate hematopoietic stem cells. *Blood* 116:1422–1432.
22. Okabe M, M Ikawa, K Kominami, T Nakanishi and Y Nishimune. (1997). 'Green mice' as a source of ubiquitous green cells. *FEBS Lett* 407:313–319.
23. Gabrilovich D, T Ishida, T Oyama, S Run, V Kravtsov, S Nadaf and DP Carbone. (1998). Vascular endothelial growth factor inhibits the development of dendritic cells and dramatically affects the differentiation of multiple hematopoietic lineages *in vivo*. *Blood* 92:4150–4166.
24. Sugiyama T, H Kohara, M Noda and T Nagasawa. (2006). Maintenance of the hematopoietic stem cell pool by CXCL12/CXCR4 chemokine signaling in bone marrow stromal cell niches. *Immunity* 25:977–988.
25. Petit I, M Szpyer-Kravitz, A Nagler, M Lahav, A Peled, L Huber, T Ponomaryov, RS Taichman, F Arencibia-Seisdedos, et al. (2002). G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4. *Nat Immunol* 3:687–694.
26. Ichishima YM, F Arai, K Hosokawa, H Toyama, K Takubo, T Furuyashiki, S Narimiya and T Suda. (2013). Prostaglandin E(2) regulates murine hematopoietic stem/progenitor cells directly via EP4 receptor and indirectly through mesenchymal progenitor cells. *Blood* 121:1995–2002.
27. Morikawa S, Y Mabuchi, Y Kubota, Y Nagai, K Niibe, E Hiratsu, S Suzuki, C Miyazuchi-Hara, N Nagoshi, et al. (2009). Prospective identification, isolation, and systemic transplantation of multipotent mesenchymal stem cells in murine bone marrow. *J Exp Med* 206:2483–2496.
28. Winkler IG, NA Sims, AR Pettit, V Barhier, B Nowlan, F Helfawi, JJ Poulton, N van Rooijen, KA Alexander, LJ Raggatt and JP Levesque. (2010). Bone marrow macrophages maintain hematopoietic stem cell (HSC) niches and their depletion mobilizes HSCs. *Blood* 116:4815–4828.
29. Levesque JP, J Hendy, Y Takamatsu, PJ Simmons and LJ Bendall. (2003). Disruption of the CXCR4/CXCL12 chemotactic interaction during hematopoietic stem cell mobilization induced by GCSF or cyclophosphamide. *J Clin Invest* 111:187–196.
30. Brouard N, R Driessens, B Short and PJ Simmons. (2010). G-CSF increases mesenchymal precursor cell numbers in the bone marrow via an indirect mechanism involving osteoclast-mediated bone resorption. *Stem Cell Res* 5:65–75.
31. Grassinger J, B Williams, GH Olsen, DN Haylock and SK Nilsson. (2012). Granulocyte colony stimulating factor

REDUCTION OF HSPC AND MPC IN THE BM BY VEGF

- expands hematopoietic stem cells within the central but not endosteal bone marrow region. *Cytokine* 58:218–225.
32. Hoggatt J, KS Mohammadi, P Singh, AF Hoggatt, BR Chitteti, JM Speth, P Hu, BA Poteat, KN Stilger, et al. (2013). Differential stem- and progenitor-cell trafficking by prostaglandin E2. *Nature* 495:365–369.
33. Kook S, J Cho, SB Lee and BC Lee. (2013). The nucleotide sugar UDP-glucose mobilizes long-term repopulating primitive hematopoietic cells. *J Clin Invest* 123:3420–3435.
34. Chamberlain G, J Fox, B Ashton and J Middleton. (2007). Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. *Stem Cells* 25:2739–2749.
35. Koizumi N, T Yamaguchi, K Kawabata, F Sakurai, T Sasaki, Y Watanabe, T Hayakawa and H Mizuguchi. (2007). Fiber-modified adenovirus vectors decrease liver toxicity through reduced IL-6 production. *J Immunol* 178:1767–1775.
36. Liu L, Q Yu, J Lin, X Lai, W Cao, K Du, Y Wang, K Wu, Y Hu, et al. (2011). Hypoxia-inducible factor-1alpha is essential for hypoxia-induced mesenchymal stem cell mobilization into the peripheral blood. *Stem Cells Dev* 20:1961–1971.
37. Pitchford SC, RC Furze, CP Jones, AM Wengner and SM Rankin. (2009). Differential mobilization of subsets of progenitor cells from the bone marrow. *Cell Stem Cell* 4:62–72.

Address correspondence to:
Dr. Kenji Kawabata
Laboratory of Stem Cell Regulation
National Institute of Biomedical Innovation
7-6-8, Saito-Azagi
Ibaraki, Osaka 567-0085
Japan
E-mail: kawabata@nibio.go.jp

Received for publication September 27, 2013
Accepted after revision December 16, 2013
Prepublished on Liebert Instant Online XXXXX XX, XXXXX

