of an electropositive patch, with P4 contacting a conserved charged region on Xrn1's winged helix domain.

This putative P4-Xrn1 interaction could serve to stabilize the xrRNA's pseudoknot interaction and thus enhance resistance to the enzyme, or P4 may form sequence-specific interactions with Xrn1 or with Xrn1-bound proteins. Also, because the winged helix domain is important for processive Xrn1 function (*29*), the bound ZIKV xrRNA may prevent conformational changes in the enzyme that are important for processivity. The new structure and derived hypotheses point the way to future studies that may clarify the formation and function of ZIKV sfRNAs, with implications for the development of interventions or vaccines.

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SUPPLEMENTARY MATERIALS

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HEMATOPOIESIS

Depleting dietary valine permits nonmyeloablative mouse hematopoietic stem cell transplantation

Yuki Taya,[1] Yasunori Ota,[2] Adam C. Wilkinson,[1,3] Ayano Kanazawa,[1] Hiroshi Watarai,[4,5] Masataka Kasai,[1] Hiromitsu Nakauchi,[1,3]* Satoshi Yamazaki[1]*

A specialized bone marrow microenvironment (niche) regulates hematopoietic stem cell (HSC) self-renewal and commitment. For successful donor-HSC engraftment, the niche must be emptied via myeloablative irradiation or chemotherapy. However, myeloablation can cause severe complications and even mortality. Here we report that the essential amino acid valine is indispensable for the proliferation and maintenance of HSCs. Both mouse and human HSCs failed to proliferate when cultured in valine-depleted conditions. In mice fed a valine-restricted diet, HSC frequency fell dramatically within 1 week. Furthermore, dietary valine restriction emptied the mouse bone marrow niche and afforded donor-HSC engraftment without chemoirradiative myeloablation. These findings indicate a critical role for valine in HSC maintenance and suggest that dietary valine restriction may reduce iatrogenic complications in HSC transplantation.

Although much is known about the molecules and signaling pathways regulating hematopoietic stem cells (HSCs), our understanding of the HSC bone marrow (BM) niche is less clear. The availability of niche "space" appears to be a limiting factor for engraftment in HSC transplantation (HSCT) (*1*). Ionizing radiation and/or high-dose chemotherapy are most commonly used to empty the BM niche. However, severe side effects limit the success of these treatments. Young patients are particularly at risk of experiencing late effects, including secondary malignancy, endocrinopathy, and reproductive failure (*2*).

[1]Division of Stem Cell Therapy, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, University of Tokyo, Tokyo 108-8639, Japan. [2]Department of Pathology, Research Hospital, The Institute of Medical Science, University of Tokyo, Tokyo 108-8639, Japan. [3]Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Lorry I. Lokey Stem Cell Research Building, 265 Campus Drive, Stanford, CA 94305-5461, USA. [4]Division of Stem Cell Cellomics, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, University of Tokyo, Tokyo 108-8639, Japan. [5]Impulsing Paradigm Change through Disruptive Technologies Program (ImPACT), Japan Science and Technology Agency (JST), Tokyo 102-0076, Japan.
***Corresponding author. Email: y-sato4@ims.u-tokyo.ac.jp (S.Y.); nakauchi@stanford.edu (H.N.)**

Numerous cellular and molecular components of the HSC niche have previously been proposed (*3*). These include several stromal and neuronal cell types, as well as various signaling molecules including the cytokines stem cell factor and thrombopoietin. In 1946, Kornberg *et al.* reported that rats fed a low-protein diet developed severe granulocytopenia or anemia that was corrected by administration of purified amino acids (AAs) (*4*, *5*). On the basis of these findings, we hypothesized that specific AAs may be indispensable for the BM niche and could influence HSC fate.

We initially quantified AA concentrations in BM and peripheral blood (PB) by high-performance liquid chromatography (HPLC). The BM contained >100-fold higher concentrations of all 20 AAs and also displayed a distinct AA profile (or AA balance), as compared with the PB (fig. S1, A and B).

To identify the specific AAs essential for the maintenance of hematopoiesis, $CD34^{-}Kit^{+}Sca1^{+}Lin^{-}$ cells (HSCs) (*6*) were cultured for 1 week in various media lacking single AAs (Fig. 1A and fig. S1C). Proliferation was significantly retarded when cysteine or valine was absent (–Cys, –Val) (Fig. 1B and fig. S2A). We also carried out similar analyses using $CD34^{+}Kit^{+}Sca1^{+}Lin^{-}$ hematopoietic progenitor cells (HPCs). HPCs displayed significant growth retardation in medium lacking cysteine or lysine (fig. S2, B and C). Growth of HPCs

was not appreciably inhibited in medium lacking valine. To determine AA requirements for HSC maintenance, we conducted competitive repopulation assays following in vitro culture (Fig. 1A). No engraftment was detected in mice that received –Cys or –Val cultured HSCs (Fig. 1C).

To assess whether –Cys and –Val media caused reactive oxygen species stress in HSCs, cellular proliferation was determined after in vitro culture in the presence of the antioxidant *N*-acetyl cysteine (NAC). NAC rescued HSC growth in –Cys medium but not in –Val medium (fig. S3). We also failed to identify significant differences in autophagy between HSCs cultured in complete and –Val media (fig. S4). Collectively, these findings support the idea that cysteine and valine are required for HSC survival and HSC self-renewal, respectively.

To investigate how cysteine and valine contribute to hematopoiesis in vivo, mice were fed complete, –Cys, or –Val diets for 4 weeks (fig. S5A). Complete blood counts revealed a significant reduction in white blood cell (WBC) and red blood cell numbers in mice fed a –Val diet (Fig. 2A), whereas platelet counts were unaffected. No differences were observed in mice fed a –Cys diet. To confirm the effect of the AA-deficient diets, we quantified AA levels in PB and BM serum by HPLC. Although cysteine levels were too low to detect, valine concentration decreased by 90% (fig. S5B). Cysteine is a nonessential AA and can be generated from the catabolism of methionine in vivo (*7*). Given this compensation, we focused on valine in our additional studies.

To further understand the effect of dietary valine restriction, we quantified various hematopoietic cell types within the PB and BM. Corresponding with our in vitro data, HSC frequencies (both immunophenotypically defined $CD34^-KSL$ HSCs and $CD150^+CD41^-CD48^-KSL$ HSCs; two

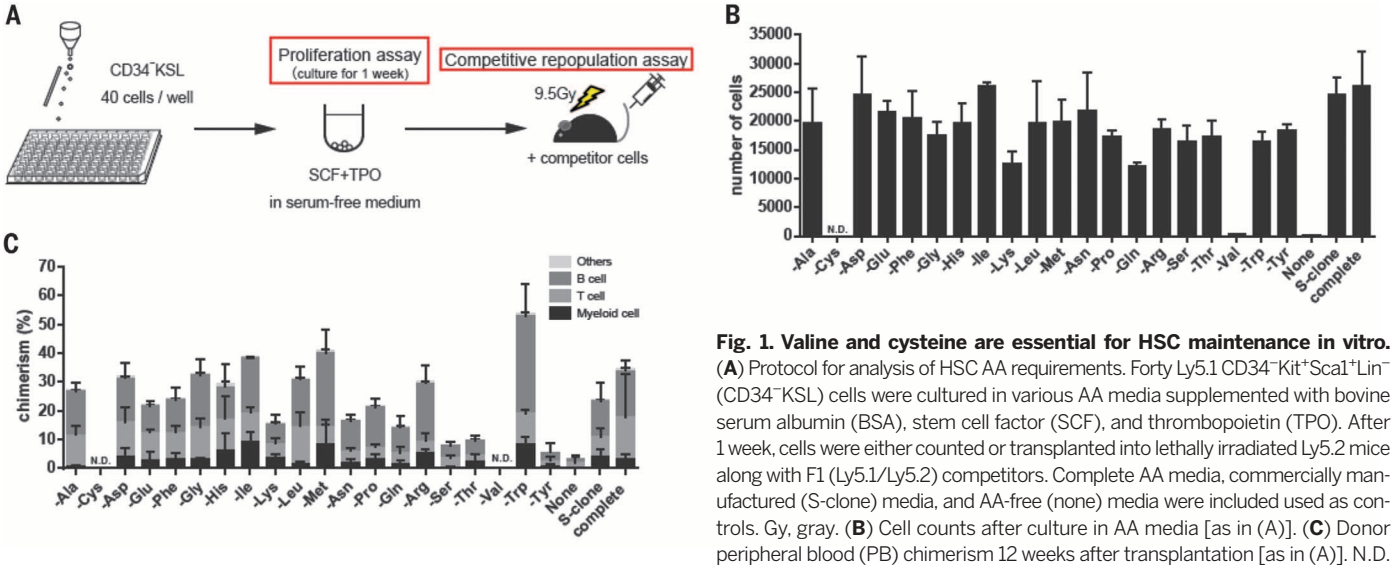


Fig. 1. Valine and cysteine are essential for HSC maintenance in vitro. (**A**) Protocol for analysis of HSC AA requirements. Forty Ly5.1 $CD34^-Kit^+Sca1^+Lin^-$ ($CD34^-KSL$) cells were cultured in various AA media supplemented with bovine serum albumin (BSA), stem cell factor (SCF), and thrombopoietin (TPO). After 1 week, cells were either counted or transplanted into lethally irradiated Ly5.2 mice along with F1 (Ly5.1/Ly5.2) competitors. Complete AA media, commercially manufactured (S-clone) media, and AA-free (none) media were included used as controls. Gy, gray. (**B**) Cell counts after culture in AA media [as in (A)]. (**C**) Donor peripheral blood (PB) chimerism 12 weeks after transplantation [as in (A)]. N.D. denotes nondetected chimerism. For (B) and (C), experiments were performed in triplicate; error bars indicate ± SD.

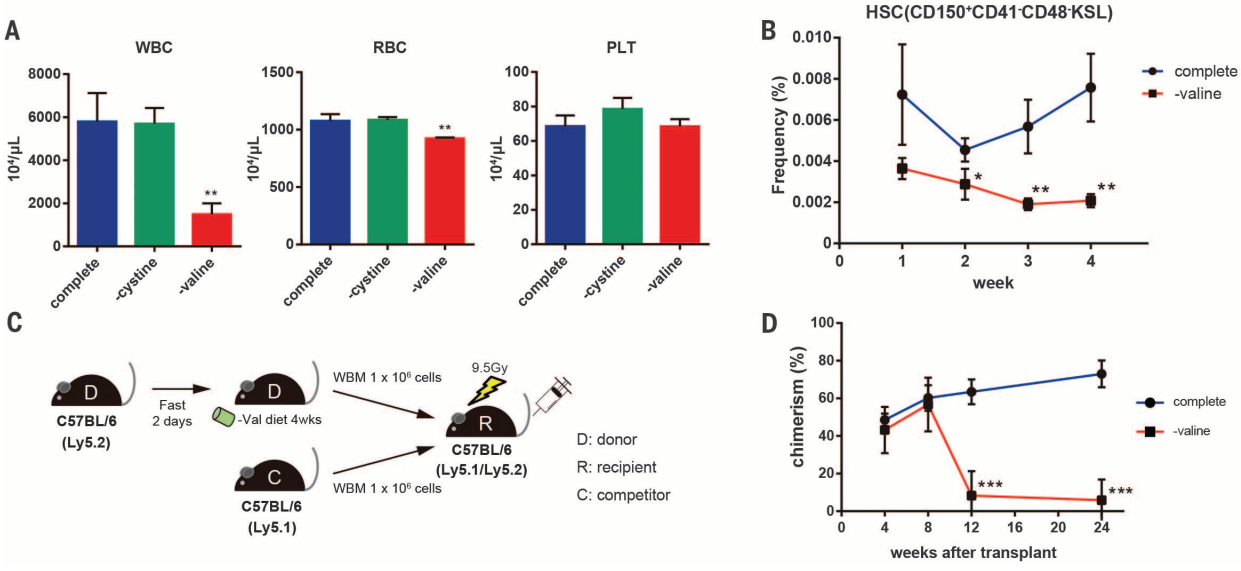
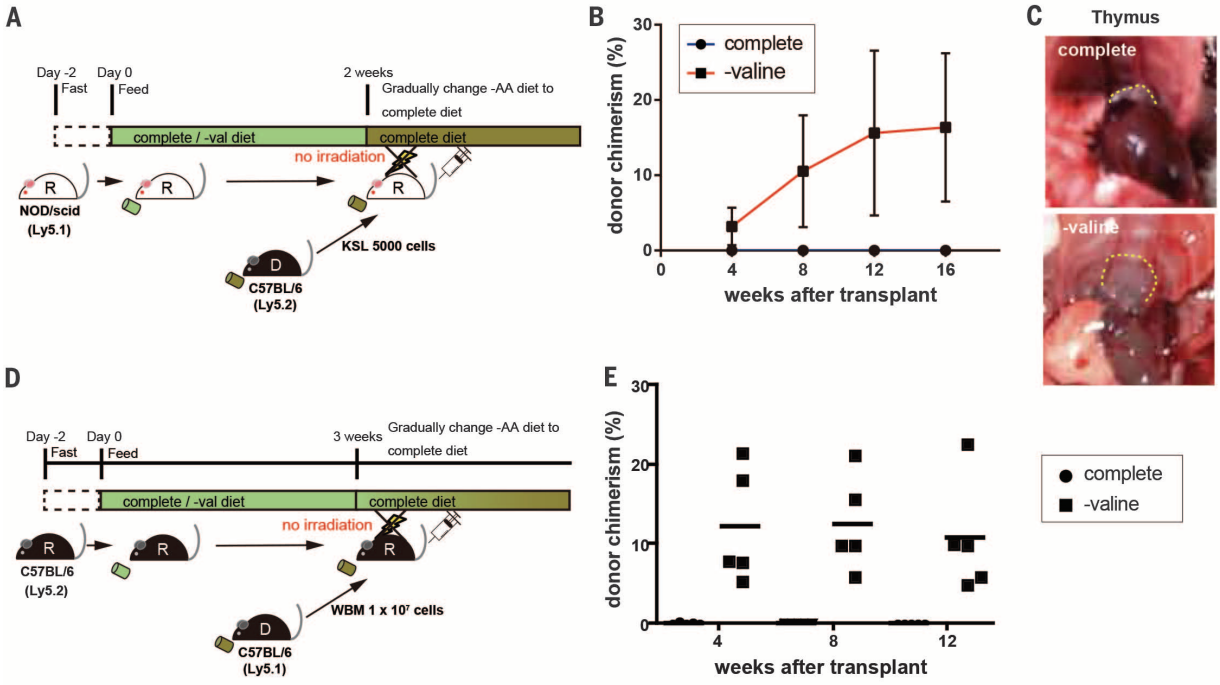


Fig. 2. Dietary valine restriction significantly perturbs hematopoiesis. (**A**) White blood cell (WBC), red blood cell (RBC), and platelet (PLT) counts following a 4-week synthetic diet ($n = 3$ mice). (**B**) Frequency of BM $CD150^+CD41^-CD48^-KSL$ HSCs following a valine-deficient (–Val) diet (complete, $n = 3$; –Val, $n = 4$). (**C**) Competitive repopulation assay protocol. BM cells from Ly5.1 mice fed a complete diet or a –Val diet for 4 weeks were transplanted into lethally irradiated Ly5.2 mice, along with an equal number of F1 competitor BM cells. WBM, whole bone marrow. (**D**) PB donor chimerism after transplantation ($n = 6$), as outlined in (C). For (A), (B), and (D), $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.



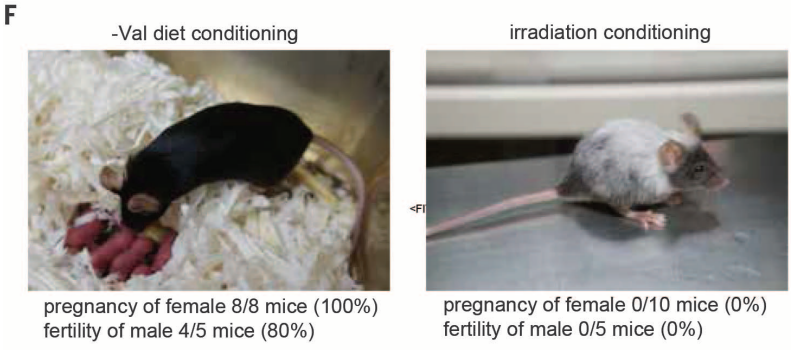


Fig. 3. Valine starvation permits HSC transplantation without irradiation. (**A**) Nonirradiative HSC transplantation into immunocompromised mice. NOD/scid mice fed a complete diet or a –Val diet for 2 weeks were transplanted, with 5×10^3 B6 donor KSL cells isolated, without irradiative conditioning. Complete diets were then returned, and donor PB chimerism was monitored. Engraftment is defined as >1% donor chimerism. (**B**) Donor chimerism after nonirradiative transplantation in NOD/scid mice, as outlined in (A) (complete group, $n = 5$; –Val group, $n = 6$). Error bars indicate ±SD. (**C**) Representative images of the thymus (yellow dotted line) in recipient mice at 12 weeks after nonirradiative transplantation. (**D**) Nonirradiative HSC transplantation into congenic mice. Ly5.2 mice fed a complete diet or a –Val diet for 3 weeks were transplanted with 1×10^7 Ly5.2 whole BM cells, without irradiative conditioning. Complete diets were then gradually returned over 2 weeks, and donor PB chimerism was monitored. Engraftment is defined as >1% donor chimerism. (**E**) Donor chimerism after nonirradiative transplantation, as outlined in (D) (complete group, $n = 5$; –Val group, $n = 5$). (**F**) Images of mice fed a –Val diet (left) or irradiation conditioned (right) 4 months after transplantation.

independent methods to define immunophenotypic HSCs) (*8*) were markedly decreased in mice fed a –Val diet (Fig. 2B and fig. S6, A to C). However, the proportion of HSCs in G_0 did not differ (fig. S6, D and E). Within the PB, numbers of $B220^+$ B cells and $CD3^+$ T cells significantly decreased (fig. S7, A and B). Additionally, cellular frequency decreased for BM B cells, common myeloid progenitor cells, and common lymphoid progenitor cells but not for BM T cells, granulocyte-monocyte progenitor cells, or megakaryocyte-erythroid progenitor cells (*9*) (figs. S7, C to E, and S8). These in vivo data indicate that HSCs display greater sensitivity than HPCs to dietary valine but that other cell populations are also affected.

To characterize the systemic effects of the valine-free diet, we histologically evaluated all organs and tissues. As expected, the BM was hypocellular, and the spleen and thymus were atrophic (fig. S9, A to C). We also observed decreased hair follicle density and a marked increase in brown fat cells in several tissues (fig. S9D). However, no obvious changes were evident in the brain, heart, lung, kidney, stomach, pancreas, or testis. Switching mice back to a complete diet brought a rapid recovery in body weight and in lymphoid populations and tissues (figs. S8 and S10, A and B). Phenotypic HSC frequencies also recovered, as well as BM HPC and $lineage^+$ populations (fig. S10, C to E). Half of the mice fed a –Val diet for 4 weeks died within days of resuming a complete diet. Autopsy identified pulmonary edema, with thickened alveolar walls and fluid-filled alveolar lumina, consistent with refeeding syndrome (*10*) (fig. S10F). Refeeding syndrome is well described in human patients, where refeeding following prolonged fasting or malnourishment can cause fatality.

Next, competitive transplantation assays were performed to determine HSC function following in vivo valine deficiency (Fig. 2C). HSCs from mice fed a –Val diet for 4 weeks were transplanted into lethally irradiated recipients, along with equal numbers of recipient BM cells. Donor chimerism was only slightly decreased for –Val cells 4 to 8 weeks after transplantation but fell sharply at 12 weeks (Fig. 2D and fig. S10G). These data indicate that dietary valine restriction depletes long-term repopulating HSCs rather than shorter-lived HPCs, consistent with our phenotypic and in vitro analyses.

Because mice fed a –Val diet had far fewer BM HSCs, we hypothesized that dietary valine restriction could empty the HSC niche and thereby replace the myeloablative conditioning regimens normally required for successful HSCT. To test this hypothesis, we set up a mouse model of allogenic HSC transplantation in immunodeficient (NOD/Scid) recipients (Fig. 3A). After transplantation of 5000 $Kit^+Sca^+Lin^-$ cells, all mice on the –Val diet survived and displayed good engraftment (Fig. 3B and fig. S11A), with markedly

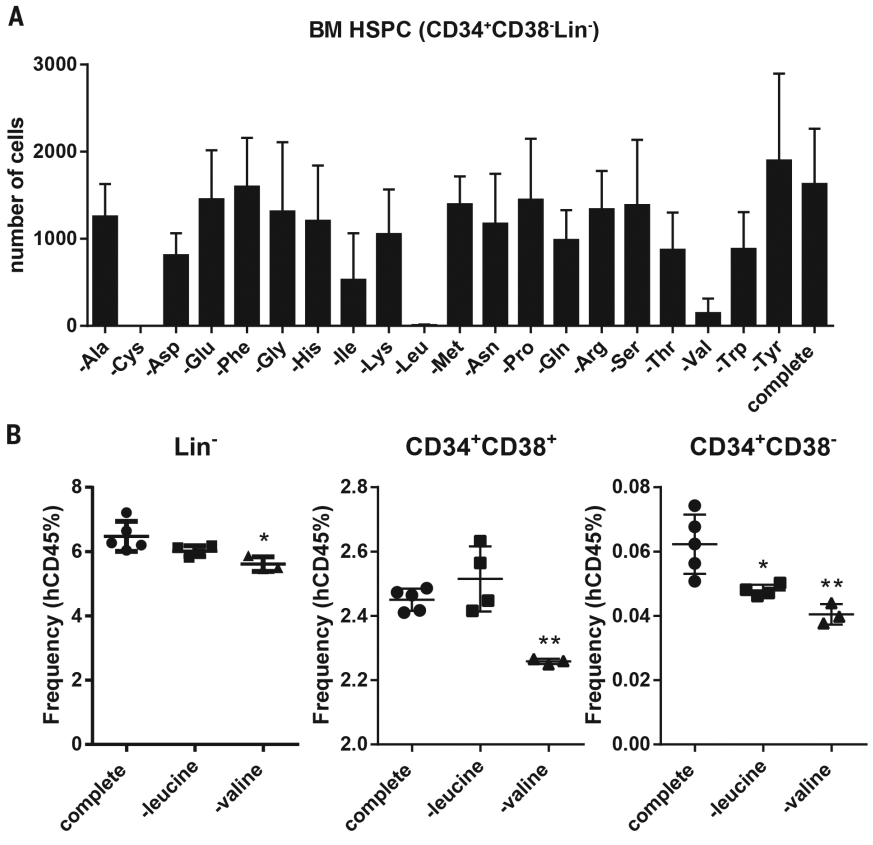


Fig. 4. Human HPSCs are sensitive to AA restriction. (**A**) One hundred human HSPCs were cultured with BSA and SCF/TPO/Flt3L/IL-3/IL-6 in complete medium (containing all AAs) or medium lacking single AAs and were counted after 7 days. Experiments were performed in triplicate. Error bars indicate ±SD. (**B**) Analysis of HSPC fractions (Lin^-, $CD34^+CD38^+$, and $CD34^+CD38^-$) in humanized mice fed a complete (n = 5), –Leu (n = 4), or –Val (n = 3) diet for 2 weeks. *P < 0.05; **P < 0.01.

increased thymus size (Fig. 3C) and gain of discrete splenic white and red pulp (fig. S11B), indicating lymphoid reconstitution.

We also transplanted 1×10^7 donor BM cells into nonirradiated congenic mice fed a –Val diet for 3 weeks. To avoid refeeding syndrome-associated mortality, valine was gradually returned to the diet over 2 weeks after the transplantation (Fig. 3D). Although no engraftment occurred in mice fed a complete diet, 5 of 5 mice displayed long-term donor chimerism following the –Val diet over 3 months after transplantation (Fig. 3E). Two further independent experiments using the same strategy showed long-term engraftment in 5 of 5 and 3 of 5 mice, and no mice died (fig. S11, C and D). HSC engraftment was confirmed by secondary transplantation assays (fig. S11E). Irradiation of recipient mice in HSC transplantation assays causes growth retardation, hair loss, and infertility, and even successfully engrafted mice usually do not survive more than a year after transplantation. By contrast, mice that received a –Val pretreatment diet appeared healthy, were fertile, and lived more than a year (Fig. 3F). Nonirradiative engraftment could also be achieved when mice were switched back to a complete diet immediately rather than gradually, but this led to significant mortality (only 10 of 26 mice survived over the long term) due to refeeding syndrome (fig. S12).

To learn whether similar AA requirements existed for human hematopoietic stem and progenitor cells (HSPCs), we used various AA-deficient media to assess the colony-forming ability of human BM $CD34^+CD38^-$ cells (*11*, *12*) (Fig. 4A and fig. S1D). As with mouse HSCs, no colonies formed under –Cys conditions, and Val deficiency suppressed cellular proliferation. Notably, –Leu conditions also decreased human HSPC proliferation (Fig. 4A).

We also tested –Val and –Leu diets on human hematopoiesis using NOD/Shi-scid/IL-2Rγ^{null} (NOG) mice reconstituted with BM $CD34^+$ cells at nearly 100% human chimerism (*11*, *12*). In mice that received –Val or –Leu diets, absolute numbers of human PB WBCs, BM cells, and $CD34^+CD38^-$ cells decreased (Fig. 4B and fig. S11, F and G). The –Val diet also significantly reduced the human Lin^- and $CD34^+CD38^+$ cell frequency, a finding that was not observed after administration of the –Leu diet (Fig. 4B). These data suggest that valine is also indispensable for human HSPC maintenance and that only valine deprivation exerts a consistent effect on mouse and human HSCs. However, the reason for this valine specificity is not clear. An AA imbalance, rather than changes in the level of a single AA, may exert such an effect in vivo, as previously proposed (*13*, *14*).

Our data indicate that HSC homeostasis relies on valine. Presumably, BM AA levels are optimal for HSC maintenance and are regulated by niche components. We therefore sought to identify AA secreted by representative niche candidates in vitro (*3*, *15*, *16*). The vascular endothelium specifically secreted Thr, Glu, Val, Leu, Ala, and Lys, whereas $PDGFR^+$ cells (platelet-derived growth factor receptor–positive) secreted Thr, Tyr, and Val (fig. S13). These results suggest that secretion of valine, and of other AAs, may be an important function of BM niche cells.

Our study highlights an important role for the AA microenvironment in hematopoiesis. Although the mechanism underlying the HSC-specific valine sensitivity remains elusive, these findings suggest a way to further understand stem cell niche functions. In addition, dietary valine restriction may be applicable for pretreatment in HSCT and the treatment of hematological malignancies.

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SUPPLEMENTARY MATERIALS

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Depleting dietary valine permits nonmyeloablative mouse hematopoietic stem cell transplantation

Yuki Taya, Yasunori Ota, Adam C. Wilkinson, Ayano Kanazawa, Hiroshi Watarai, Masataka Kasai, Hiromitsu Nakauchi and Satoshi Yamazaki

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How to maintain hematopoietic stem cells

Hematopoiesis provides the body with a continuous supply of blood cells (see the Perspective by Sommerkamp and Trumpp). Taya *et al.* report that amino acid content is important for hematopoietic stem cell (HSC) maintenance in vitro and in vivo. Dietary valine restriction seems to "empty" the mouse bone marrow niche. Ito *et al.* used single-cell approaches and cell transplantation to identify a subset of HSCs at the top of the HSC hierarchy. Self-renewal relied on the induction of mitophagy, a quality-control process linked to a cell's metabolic state. Both studies may be helpful in improving clinical bone marrow transplantation.

Science, this issue p. 1103, p. 1152; see also p. 1156