Supplemental methods

Induction of phenylhydrazine induced acute hemolytic anemia[34] and isolation PBMCs. 6 to 8-week-old C57BL/6 mice (Taconic) were injected with a single dose of phenylhydrazine (100mg/kg mouse in sterile PBS). Peripheral blood was isolated by cardiac puncture at the indicated time points and diluted into sterile PBS. The diluted peripheral blood cells were layered onto Histopaque 1077 (Sigma-Aldritch) and centrifuged. Peripheral blood mononuclear cells (PBMCs) were isolated from the interface and washed twice in PBS + 2% fetal bovine serum.

Stress erythropoiesis cultures. Stress erythropoiesis cultures were performed as previously done[34, 44]. In short, PBMCs were cultured in stress erythropoiesis differentiation media (SEDM) containing IMDM media supplemented with 20% fetal bovine serum + Shh (25ng/mL) + BMP4 (15ng/mL) + GDF15 (30ng/mL) + SCF (15ng/mL) + Epo (3ng/mL) and cultured at 2%O2 for 5 days. Nonadherent progenitor cells were assayed for stress BFU-E formation by plating 1 x 10^5 expanded cells/ mL of methylcellulose media (M3334 StemCell Technologies, Vancouver, BC, Canada), which contains 3 U/mL Epo. BFU-E colonies were stained with acid benzidine stain and counted after 5-7 days of culture. Total number of BFU-E in the expanded cells was calculated.

Isolation of PBMCs from Sickle cell anemia patients. De-identified peripheral blood samples from patients suffering from sickle cell disease was obtained from Case Western Reserve University Hospital. PBMCs were then isolated from peripheral blood using Histopaque 1077 as described above for murine PBMCs. Control PBMCs were

524 purchased from ReachBio. PBMCs obtained were plated at 1 x 10^6 cells/ml stress
525 erythropoiesis differentiation media containing human growth factors. The cells were
526 cultured for 5 days at 2% O_2. After 5 days of culture, the expanded nonadherent
527 progenitor cells were plated at 1x10^5 cells per ml in methylcellulose media (H4330
528 StemCell Technologies, Vancouver, BC, Canada) for assay of stress BFU-E colony
529 formation. After 5 days of culture, colonies were stained with acid benzidine and
530 counted. Total number of BFU-E in the expanded cells was calculated.

531 **Flow cytometric analysis of human PBMCs.** Prior to culture in SEDM media and after
532 5 days of culture in SEDM, human PBMC were analyzed for the expression of KIT,
533 CD34 and CD133 as previously described[44].

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