EXTENDED EXPERIMENTAL PROCEDURES

Bone Marrow Cellularity

Femurs were dissected and flushed with 5 ml phosphate buffered saline (PBS) supplemented with 2% fetal bovine serum (FBS, Mediatech). Cells were resuspended by pipetting and vortexing. White blood cell counts were obtained by VetScan HM5 instrumentation (Abaxis Veterinary Diagnostics).

Generation of ANG and anti-ANG antibodies

Mouse and human recombinant ANG protein were generated by a pET *E. coli* expression system and purified to homogeneity by HPLC in-house (Shapiro et al., 1988). Angiogenic and ribonucleolytic activity of each batch of ANG preparation was confirmed (data not shown). ANG variants (R33A, K40Q, and R70A) were generated through site-directed mutagenesis followed by expression in pET system and purification by HPLC. Monoclonal (C527) and polyclonal (R163) antibodies against mouse ANG were generated in-house.

In Vitro and *In Vivo* ANG Treatment

Unless otherwise indicated (in dose response experiments), 300 ng/ml ANG was used for *in vitro* treatments. For all *in vivo* ANG treatments, 1.25 mg/kg was injected intraperitoneally at the indicated time points.

5-Fluorouracil (5-FU) Treatment

For 5-FU rebound experiments, 5-FU (150 mg/kg) was injected intraperitoneally once and BM harvested for analysis on Day 7. For serial 5-FU treatments, 5-FU (150 mg/kg) was injected intraperitoneally every 7 days until 100% animal mortality was achieved.

Histology

Femurs were dissected from animals and fixed overnight in 10% neutral buffered formalin. Bones were prepared, decalcified, and stained with Hematoxylin and Eosin (H&E) by the Tufts Animal Histology Core.

Genotyping

Genotyping was performed by PCR with Hot Start Green PCR Master Mix (Thermo Scientific), using standard PCR conditions on an iCycler PCR machine (Biorad). The *Ang* primers for *Ang*$^{-/-}$ mice were as follows: Forward, 5'- AGCGAATGGAAGCCCTTACA-3'; reverse, 5'-CTCATCGAAGTGGACAGGCA-3'. The primers for the LoxP site (F12/B6) were as follows: Forward, 5'-AGGGTGGAACTTCAGGATTCAAG-3'; reverse, 5'-GAAGTTATCCGCGGGAAGTTC-3'.

Complete Blood Counts

Peripheral blood was harvested from mice by retro-orbital bleeding using heparinized micro-hematocrit capillary tubes (Fisherbrand). Blood was collected directly into EDTA-coated Microtainer tubes (BD) and automated complete blood counts were assessed by VetScan HM5 instrumentation.

Flow Cytometry and Cell Sorting

Whole bone marrow mononuclear cells (BMMNC) were obtained by crushing tibias and femurs in PBS/2% FBS and straining cellular suspension through 0.45 μm mesh. Red blood cells were depleted using ACK Lysis Buffer (Lonza). Briefly, 2 ml buffer was added to cell pellet and incubated on ice for 5 minutes with periodic vortexing. Cells were washed once and resuspended in 200 μl PBS/2% FBS for staining using 1:200 dilutions of primary antibodies unless otherwise indicated.

For stem and progenitor staining, red cell-depleted BMMNCs were stained with antibodies against cKit BV711 (BD), Sca1 PE-Cy5 (eBioscience), Flk2 PE (BD), CD34 e660 (eBioscience), IL7R APC-Cy7 (eBioscience), B220 BV785 (Biolegend), CD16/32 AF700 (eBioscience) and a biotinylated lineage cocktail (B220, CD3, CD4, CD8, Mac1, and Ter119 at 1:1:1:1:1:1). Cells were stained for 90 minutes on ice, followed by streptavidin PE-Cy7 (Biolegend) for 15 minutes on ice. Cells were analyzed using a FACSAria flow cytometer (BD).

For Slam marker staining, red cell-depleted BMMNCs were stained with antibodies against cKit BV711, Sca BV421 (Biolegend), CD150 PE-Cy7 (Biolegend, 1:100), CD48 APC-Cy7 (BD, 1:400), and a biotinylated lineage cocktail. Cells were stained for 90 minutes on ice, followed by streptavidin Pacific Orange (Invitrogen) for 15 minutes on ice.

For lineage analysis, red cell-depleted BMMNCs were stained for 30 minutes on ice with antibodies against CD11b PE-Cy7 (Biolegend), Gr1 PE (eBioscience, 1:400), CD45R/B220 FITC (BD), CD3ε APC-Cy7 (Biolegend), and Ter119 APC (eBioscience). Cells were analyzed using a LSRII flow cytometer (BD).

For chimerism studies, peripheral blood was obtained by retro-orbital bleeding and depleted of red blood cells. Samples were stained for 30 minutes on ice with antibodies against CD45.1 APC (eBioscience), CD45.2 Pacific Blue (Biolegend), CD11b PE-Cy7, Gr1 PE, CD45R/B220 FITC, and CD3ε APC-Cy7. Cells were analyzed using a LSRII flow cytometer.

For sorting LKS cells or myeloid-restricted progenitors, red cell-depleted BMMNCs were stained with antibodies against cKit APC (eBioscience), Sca1 PE (eBioscience), and a FITC lineage cocktail for 30 minutes on ice. Cells were sorted using FACSAria or MoFlow Astrios (Beckman Coulter) flow cytometers.

For sorting LT-HSCs, red cell-depleted BMMNCs were stained with antibodies against cKit APC-eF780 (eBioscience), Sca1 PE-Cy5, Flk2 PE, CD34 e660, and a biotinylated lineage cocktail. Cells were stained for 90 minutes on ice, followed by streptavidin PE-Cy7 (Biolegend) for 15 minutes on ice. Cells were sorted using a FACSAria flow cytometer.

For all analyses, 4',6-diamidino-2-phenylindole (DAPI, Molecular Probes) or 7-aminoactinomycin d (7-AAD, BD) were used as viability dyes, per manufacturer's instructions. At least 2×10^6 events per sample were acquired for bone marrow stem and progenitor analysis and 3×10^4 events for lineage analysis. Data were analyzed using FlowJo X (Tree Star).

Cell Cycle Analysis
For cell cycle, 1 x 10^7 red cell-depleted BMMNCs were stained with cell surface markers fixed and permeabilized using Cytofix/Cytoperm Fixation/Permeabilization Kit (BD) per manufacturer's instructions. Cells were then stained with Ki67 FITC (BD, 1:10 in BD Perm/Wash buffer) and DAPI (2 μg/ml for 10 minutes prior to analysis), and analyzed using a FACSAria flow cytometer, acquiring 2 x 10^6 events per sample. The percentage of quiescent and cycling LT-HSC in WT mice were ~50% and ~7% by both Flk and Slam markers, in keeping with those previously reported (Heidt et al., 2014; Krock et al., 2015; Passegue et al., 2005).

BrdU Incorporation
BrdU was administered in drinking water (0.35 mg/ml) for 3 days (Doan et al., 2013; Heidt et al., 2014; Liu et al., 2009; Winkler et al., 2012). Volume of drinking water was assessed to confirm equal water intake among cages. Mice were sacrificed and red cell-depleted BMMNCs were stained with antibodies against cell surface markers (1:200) as follows:

For HSPCs, cells were stained with c-Kit APC-eF780, Sca1 PE-Cy5, Flk2 PE, CD34 e660 and a biotinylated lineage cocktail. Cells were stained for 90 minutes on ice, followed by streptavidin Pacific Orange for 15 minutes on ice.

For lymphoid-restricted progenitors, cells were stained with c-Kit APC-eF780, Sca1 PE-Cy7 (Biolegend), IL7R PE (eBioscience), B220 PE-Cy5 (eBioscience), and a biotinylated lineage cocktail. Cells were stained for 90 minutes on ice, followed by streptavidin Pacific Orange for 15 minutes on ice.

For myeloid-restricted progenitors, cells were stained with c-Kit APC-eF780, Sca1 PE-Cy5, CD16/32 BV605 (BD), CD34 e660 and a biotinylated lineage cocktail. Cells were stained for 90 minutes on ice, followed by streptavidin Pacific Orange for 15 minutes on ice.

Following cell surface stain, cells were fixed and permeabilized, and stained with BrdU FITC (BD), per manufacturer's instructions. For all stains, cells were analyzed using a FACSAria flow cytometer, acquiring 2 x 10^6 events per sample. BrdU gating was established by cells isolated from mice not administered BrdU and BrdU fluorescence-minus-one controls.

Annexin V Analysis
To assess apoptotic activity, red cell-depleted BMMNCs were stained for cell surface markers as above, and stained with Annexin V FITC (BD), per manufacturer's instructions. Briefly, cells were resuspended in 1x Binding buffer (BD) at 1 x 10^6 cells/ml and stained for 15 min at room temperature (RT) in the dark. Four hundred μl of 1x Binding buffer was added to each tube analyzed on a LSRII or FACSAria flow cytometer within 1 hour. Annexin V-positive gates were established by Annexin V fluorescence-minus-one controls.

Mouse and Human Methylcellulose Colony Assays
For myeloid progenitor quantification, 2 x 10^4 whole BMMNCs were plated in MethoCult M3434 methylcellulose (Stem Cell Technologies), per manufacturer's instructions. Colonies were scored by visualization on Day 12.

For serial re-plating assays, 2 x 10^4 whole BMMNCs were plated in MethoCult M3434 methylcellulose and colonies were scored at Day 7. Colonies were the harvested, per manufacturer's instructions, 2 x 10^4 whole BMMNCs were again plated in methylcellulose. Colonies were subsequently scored on Day 14.

For pre-pro B progenitor quantification, 5 x 10^4 whole BMMNCs were plated in MethoCult M3630 methylcellulose (Stem Cell Technologies), per manufacturer's instructions. Colonies were scored by visualization on Day 7.

For human progenitor quantification, 2 x 10^4 human $CD34^+$ cord blood cells (Stem Cell Technologies, mixed donors) were plated in MethoCult H4034 methylcellulose in the presence or absence of 300 ng/ml human ANG. Colonies were scored by visualization on Day 15.

All assays were cultured in untreated 35-mm culture dishes (Stem Cell Technologies) and maintained for the duration of the experiment at 37°C/5% CO_2, per manufacturer's instructions. For all experiments, data were presented as frequency of total number of plated cells.

Quantitative RT-PCR Analyses

Total RNA was extracted from sorted or treated hematopoietic cell populations using RNeasy Plus Micro Kit (Qiagen), and was reverse transcribed into cDNA with Quantitech Reverse Transcription Kit (Qiagen), per manufacturer's instructions. For analysis of *Ang* expression in niche cells and central BM, whole BM cells were isolated from femur and tibiae by flushing. Total RNA was extracted by Trizol. For analysis of niche cells, bones were flushed 2 additional times with PBS and were then flushed with 1 ml Trizol directly. Total RNA was reversely transcribed into cDNA by M-MLV reverse transcriptase (Promega). For qRT-PCR analysis of rRNA species, random primers (IDT) were used during reverse transcription. For all other analyses, Oligo(d)T primers (IDT) were used. qRT-PCR analysis was performed on a LightCycler 480 II (Roche) using SYBR Green PCR mix (Roche). Relative expression was determined by the $2^{-\Delta\Delta Ct}$ method, using β-actin as an internal control. Primer sequences were adapted from the following sources: mouse Ang (Hooper et al., 2003), mouse p21, p27, and p57 (Chakkalakal et al., 2014); mouse GATA3, Bmi1, and vWF (Kent et al., 2009); mouse a1, Bcl2, Bcl-xl, Mcl1, Bak, Bax, Bid, Bim, Noxa, Puma, and β-Actin (Mohrin et al., 2010); human p21 (Zhu et al., 2011); human p27 (Bryant et al., 2006); human p57 (Giovannini et al., 2012); human GATA3 (Wang et al., 2014); human vWF (Yoon et al., 2012); human Bmi1 (Abdouh et al., 2009); human cyclin D1 (Ding et al., 2009); and human β-Actin (Sheng et al., 2014). See Supplementary Tables, below, for primer information.

Mouse LT-HSC Culture

For 2 hour treatments in PBS, LT-HSCs were sorted directly into PBS and cultured in the presence or absence of 300 ng/ml ANG. For other cell proliferation and qRT-PCR analyses, LT-HSCs were sorted into 96-well plates and cultured in S-clone SF-O3 (Sanko Junyaku), supplemented with 0.5% bovine serum albumin (Gibco Life Technologies), 50 ng/ml thrombopoietin (Peprotech), 50 ng/ml stem cell factor (Peprotech) and 50 μM 2-mercaptoethanol (Gibco Life Technologies), in the presence or absence of 300 ng/ml ANG. For 2- or 7 day treatments, 1X Penicillin/Streptomycin (Corning) was included in culture medium. Cells were cultured at 37°C/5% CO_2.

For proliferation studies, cell number was determined by hemocytometer. For qRT-PCR studies, cells were harvested and analyzed as described under "Quantitative RT-PCR Analyses". For BM transplantation, cells were harvested, washed with PBS, and counted. Equal cell numbers were transplanted as described under "Mouse Bone Marrow Transplantation."

Human $CD34^+$ Cord Blood Cell Culture

Human $CD34^+$ cord blood cells (Stem Cell Technologies) were thawed per manufacturer's instructions. For 2 hour treatments, cells were cultured in PBS in the presence or absence of 300 ng/ml hANG. For 7 day culture, cells were cultured in StemSpan SFEM (Stem Cell Technologies), supplemented with stem cell factor, Flt3 ligand, IL6, and thrombopoietin (100 ng/ml, R&D), in the presence or absence of 300 ng/ml hANG. Cells were cultured at 37°C/5% CO_2. Commercial human ANG (R&D) was also tested at 300 ng/ml and shown to neither have as strong induction of candidate self-renewal transcripts nor as strong reduction in proliferation, consistent with our previous findings that the biological activity of commercial ANG is about 10% of our in house ANG preps (data not shown). Human ANG variants (K40Q, R70A, R33A) were used at the same concentration of 300 ng/ml. For proliferation studies, cell number was determined by hemocytometer. For qRT-PCR studies, cells were harvested and analyzed as described under "Quantitative RT-PCR Analyses".

Mouse Bone Marrow Transplantation

For all mouse transplant studies, recipient mice were lethally-irradiated 16 hours prior to transplantation with 12 Gy total body irradiation (TBI, split dose 3 hours apart). All mice were irradiated in a pie cage (Braintree Scientific) with rotation (JL Shepherd irradiator). For each experiment, mice from different experimental groups were simultaneously irradiated to ensure equal irradiation among groups.

For serial transplantation of LT-HSCs into ANG-deficient hosts, 400 sorted LT-HSCs from CD45.1 donor mice were co-injected with 1 x 10^6 CD45.2 whole BM support cells into lethally-irradiated WT or *Ang*$^{-/-}$ (CD45.2) recipient mice. After 24 months, BM was harvested, 400 LT-HSCs were re-sorted and transplanted again into WT or *Ang*$^{-/-}$ (CD45.2) secondary recipients with 1 x 10^6 CD45.2 whole BM support cells.

For serial transplantation of WBM into ANG-deficient hosts, 1 x 10^6 whole BM cells were transplanted into lethally-irradiated WT or *Ang*$^{-/-}$ (CD45.2) recipient mice. After 24 months, BM was harvested and 1 x 10^6 whole BM cells (CD45.1) were transplanted again into WT or *Ang*$^{-/-}$ (CD45.2) secondary recipients.

For direct 1:1 competitive transplantation studies using 22 month old WT or *Ang*$^{-/-}$ mice, 5 x 10^5 whole BMMNCs (CD45.2) were intravenously co-injected with 5 x 10^5 B6.SJL (CD45.1) support cells into lethally-irradiated B6.SJL (CD45.1) recipient mice.

For *ex vivo* reconstitution assays, WT and *Ang*$^{-/-}$ LT-HSCs (CD45.2), either freshly sorted or cultured with or without 300 ng/ml ANG for 2 hours or 7 days, were washed in PBS, and 400 donor cells were intravenously co-injected with 1 x 10^6 B6.SJL (CD45.1) support cells into lethally-irradiated B6.SJL (CD45.1) recipient mice. For secondary transplantation in *ex vivo* reconstitution assays, C57BL/6 LT-HSCs (CD45.2) were sorted from primary recipients that

were transplanted with fresh LT-HSCs or LT-HSCs treated with or without ANG for 2 hours. Four hundred LT-HSCs from primary recipients were then intravenously co-injected with 1 x 10^6 B6.SJL (CD45.1) support cells into lethally-irradiated B6.SJL (CD45.1) recipient mice.

For transplantation of tiRNA-transfected LKS cells, 3,000 sorted C57BL/6 LKS (CD45.2) were transfected as described under "tiRNA Transfection", and intravenously co-injected with 1 x 10^6 B6.SJL (CD45.1) support cells into lethally-irradiated B6.SJL (CD45.1) recipient mice.

For transplantation of irradiated BM (pre-treatment group), C57BL/6 (CD45.2) mice were pretreated daily for three successive days with ANG and irradiated (4 Gy TBI) 24 hours following the final ANG treatment. BM was harvested at Day 7, donor BMMNCs were pooled and intravenously co-injected with B6.SJL (CD45.1) support cells (1:1) into lethally-irradiated B6.SJL (CD45.1) recipient mice. For the delayed treatment group, C57BL/6 (CD45.2) mice were irradiated (4 Gy) and treated with ANG daily for three successive days, beginning 24 hours post-irradiation. BMMNCs were harvested and transplanted as in the pre-treatment group.

For all transplants, except for irradiation reconstitution assays, peripheral blood was taken by retro-orbital bleeding at 4-week time intervals, up through 16 or 24 weeks, as indicated. For irradiation assays, peripheral blood was taken by retro-orbital bleeding at 16 weeks post-transplant. Reconstitution units (RU) per femur, corresponding to the HSC content per 1 x 10^5 BM cells, was calculated as previously described (Purton and Scadden, 2007; Winkler et al., 2012).

Human CD34$^+$ Cord Blood Cell Transplantation

NSG mice were purchased from The Jackson Laboratory and maintained in sterile housing. Recipient NSG mice were sublethally irradiated (2.5 Gy TBI) 16 hours prior to transplantation. Human CD34$^+$ cord blood cells from mixed donors were treated with or without 300 ng/ml human ANG for 2 hours in PBS at 37°C/5% CO_2. Cells were washed once in PBS and intravenously injected in three doses: 100, 1,000, and 10,000 cells. Both male and female mice were used as recipients for all treatments and doses. No significant differences were observed among experimental groups between male and female mice, different from a previous report (McDermott et al., 2010). At 16 weeks post-transplant, red cell-depleted BMMNCs were surface stained with the following antibodies for 30 minutes on ice (1:200 dilution): human CD45 Pacific Blue (Biolegend), Mouse CD45 APC-e780 (eBioscience), Human CD19 PE-Cy7 (BD), Human CD33 PE (BD). Samples were analyzed using a FACSAria flow cytometer. Engraftment was assessed by the frequency of human CD45 cells. All samples demonstrating greater than or equal to 0.1% hCD45 expression were considered to be positively-engrafted, in keeping with prior studies (Boitano et al., 2010). For secondary transplantation, 5 x 10^5 BMMNCs harvested at week 16 from primary recipients (10,000 cell dose) was transplanted into sublethally irradiated recipients. No additional ANG treatment was administered.

Homing Assay

Homing assays were performed as described previously (Hoggatt et al., 2009). For homing assays using WT or *Ang*$^{-/-}$ mice as recipients, 2 x 10^6 CD45.1 Lin$^-$ cells were labeled with CFSE (Molecular Probes) per manufacturer's instructions, and transplanted into lethally-irradiated WT or *Ang*$^{-/-}$ (CD45.2) recipient mice. Cells were harvested 16 hours post-transplant, stained with

antibodies against cell-surface markers as described above, and analyzed on a FACSAria flow cytometer. Percent CFSE-positive LKS cells and myeloid-restricted progenitors was determined. For homing assays using ANG-treated cells, 2 x 10^6 CD45.2 Lin^- cells were treated with 300 ng/ml ANG in PBS for 2 hours at 37 °C/5% CO_2. Cells were labeled with CFSE, as above, and transplanted into lethally-irradiated B6.SJL (CD45.1) recipient mice. Cells were harvested 16 hours post-transplant, stained with antibodies against cell-surface markers as described above, and analyzed on a FACSAria flow cytometer. Percent CFSE-positive LKS cells and myeloid-restricted progenitors was determined.

Protein Synthesis Analyses

Determination of protein synthesis rates in BM cells was done using OP-Puro as previously described (Signer et al., 2014).

For *in vitro* analyses, LKS cells or myeloid-restricted progenitors were sorted as described above, and plated in DMEM (Sigma) in the presence or absence of 300 ng/ml ANG. Cells were cultured for 2 hours at 37°C/5% CO_2. Cells were washed once with Ca^{2+}- and Mg^{2+}-free PBS and cultured for 1 hour with OP-Puro (50 μM, Medchem Source). Cells were fixed in 0.5 ml of 1% paraformaldehyde (Affymetrix) in PBS for 15 minutes on ice, washed once with PBS, and then permeabilized with 200 μl PBS supplemented with 3% FBS and 0.1% saponin (Sigma) for 5 minutes at room temperature (RT). Click-iT Cell Reaction Buffer Kit (Life Technologies) was used for azide-alkyne cycloaddition of AF488-conjugated azide (5 μM, Life Technologies), per manufacturer's instructions. Cells were washed twice in PBS/3% FBS/0.1% saponin and analyzed using a FACSAria flow cytometer.

For *in vivo* analyses, OP-Puro was injected intraperitoneally (50 mg/kg in PBS). One hour post-injection, BM was collected from sacrificed mice and red cell-depleted BMMNCs were stained as follows. Unless otherwise indicated, primary antibodies were used at 1:200 dilution.

For stem and progenitor staining, 5 x 10^6 cells were stained with cKit BV711, Sca1 APC-Cy7 (Biolegend, 1:80), Flk2 APC (Biolegend, 1:50), CD34 e450 (eBioscience, 1:50), and a biotinylated lineage cocktail. Cells were stained for 90 minutes on ice, followed by streptavidin Pacific Orange for 15 minutes on ice.

For lymphoid-restricted progenitor staining, 5 x 10^6 cells were stained with cKit BV711, Sca1 APC-Cy7, Flk2 APC, IL7R PerCP-Cy5.5 (eBioscience, 1:80), B220 BV650 (Biolegend, 1:80) and a biotinylated lineage cocktail. Cells were stained for 90 minutes on ice, followed by streptavidin Pacific Orange for 15 minutes on ice.

For myeloid-restricted progenitor staining, 5 x 10^6 cells were stained with cKit BV711, Sca1 APC-Cy7, CD16/32 BV605 (BD. 1:80), CD34 e450 and a biotinylated lineage cocktail. Cells were stained for 90 minutes on ice, followed by streptavidin Pacific Orange for 15 minutes on ice.

For lineage staining, 5 x 10^5 cells were stained with Mac1 APC (eBioscience), Gr1 PE (1:400), CD3ε Pacific Blue (Biolegend, 1:100), and Ter119 APC-Cy7 (Biolegend, 1:100) for 30 minutes on ice.

Following surface staining, cells were washed twice with Ca^{2+}- and Mg^{2+}-free PBS and resuspended in 1 ml PBS. One µl UV-fixable eFluor 455 viability dye was added (eBioscience), cells were incubated for 30 minutes at 4°C in the dark, and washed once with PBS, per manufacturer's instructions. Following staining, cells were fixed and permeabilized and cycloaddition of AF488-conjugated azide (Life Technologies) was performed as described above. Cells were analyzed using a FACSAria flow cytometer, acquiring 2 x 10^6 events per sample for BM stem and progenitor analysis and at least 3 x 10^4 events for lineage analysis. In a separate experiment, DAPI was used for cell cycle analysis, as previously described (Signer et al., 2014).

Treated samples were compared to mice or cells not administered OP-Puro and/or OP-Puro fluorescence-minus-one controls. Relative rate of protein synthesis was determined as described previously (Signer et al., 2014). Briefly, background fluorescence was subtracted from OP-Puromycin AF488 geometric means and normalized relative to whole BM or WT controls for *in vivo* and *in vitro* experiments, respectively.

tiRNA Gel Electrophoresis

For all RNA work, equipment was sterilized according to standard laboratory protocol and diethylpyrocarbonate-treated water was used for all procedures. Total RNA was isolated and pooled from sorted LKS cells, myeloid-restricted progenitors, or lineage-positive cells for each experimental parameter. Total RNA was diluted in 2X Novex TBE-Urea sample buffer (Invitrogen), heated to 65°C for 5 minutes and cooled briefly to RT prior to loading. A 15% TBE-Urea Gel (Invitrogen) was pre-run at 74 V for 60 minutes and samples were electrophoresed to the bottom of the gel at 100 V in 0.5X TBE running buffer. A low molecular weight marker (10-100 nt, Affymetrix) was simultaneously run to compare RNA band sizes.

Following electrophoresis, the gel was equilibrated in 0.5X TBE for 5 minutes and stained with SYBR Gold solution (Invitrogen) diluted in 20 ml of 0.5X TBE buffer for 60 minutes with agitation, per manufacturer's instructions. Gels were imaged on a Kodak Electrophoresis Documentation and Analysis System 120 using UV illumination. Images were quantified by Image J software (NIH) and multiple independent experiments were normalized and averaged.
For oxidative stress experiments, cells were treated with 500 µM sodium arsenite (Sigma Aldrich) for 2 hours in the presence or absence of 300 ng/ml ANG. For irradiation experiments, WT C57BL/6 mice were irradiated with 4.0 Gy TBI. Twenty four hours post-TBI, LKS cells or myeloid-restricted progenitors were sorted and treated *in vitro* with 300 ng/ml ANG for 2 hours in PBS at 37°C/5% CO_2. For culture experiments, sorted LKS cells were either immediately stimulated with ANG or cultured for 7 days in the presence or absence of ANG in S-clone media, as indicated above. On Day 7, cells cultured in the presence or absence of ANG were harvested, washed once in PBS, and again stimulated with or without 300 ng/ml ANG for 2 hours in PBS at 37°C/5% CO_2.

Northern Blotting

Total RNA was isolated from ANG-treated LKS cells or myeloid-restricted progenitors and subjected to electrophoresis, as described above. RNA was transferred to a Pall Biodyne nylon membrane (Promega) using wet transfer. Briefly, a transfer cassette was assembled with the following pre-wet components: sponge, 3 pieces Whatman chromatography paper, gel,

membrane, 3 pieces Whatman chromatography paper, and sponge. The apparatus was then transferred in pre-chilled 0.5X TBE at 80 V for 60 minutes at 4°C. Following transfer, the apparatus was disassembled and the membrane rinsed in 1X TBE. Transfer efficiency was confirmed by post-transfer staining of the gel with SYBR Gold, as described above. RNA was fixed to the blot by baking at 80°C for 2 hours. The membrane was rinsed in pre-warmed digoxigenin (DIG) Easy Hyb buffer (Roche) for 30 minutes at 50°C with rotation and then hybridized in DIG Easy Hyb buffer containing DIG-labeled DNA Probe (IDT) at 25 ng/ml. For 5'-Gly-GCC the HPLC-purified DIG-labeled probe with the sequence of 5'-GGCGAGAATTCTACCACTGAACCACCAA-3' was used. The probe was heat-denatured for 5 minutes prior to hybridization. Following overnight hybridization, membranes were rinsed once in 2X SSC/0.1% SDS for 10 minutes at 60°C, twice in 0.5X SSC/0.1% SDS for 20 minutes at 60°C and once for 5 minutes in Washing Buffer (Roche) at RT, all with agitation. Following stringency washes, the membranes were blocked for 30 minutes, rocking at RT in blocking solution (Roche), probed with alkaline phosphatase-labeled anti-DIG antibody (Roche) for 30 minutes at RT, washed twice for 20 minutes per wash with washing buffer (Roche), equilibrated for 5 minutes in detection buffer (Roche), and visualized with CSPD (Roche), per manufacturer's instruction.

tiRNA Transfection

Active 5'-P-tiRNA-Gly-GCC (5'-P-GCAUUGGUGGUUCAGUGGUAGAAUUCUCGCCUGCC-3') was commercially synthesized (IDT). Inactive, 5'-dephosphorylated (d)5'-P-tiRNA was generated by treating active 5'-P-tiRNA with acid phosphatase (Sigma). Sorted LKS cells or myeloid-restricted progenitors were transfected with 1 μM of 5'-P-tiRNA-Gly-GCC or (d)5'-P-tiRNA-Gly-GCC in the presence of lipofectamine, as previously described (Ivanov et al., 2011; Yamasaki et al., 2009), or by electroporation in hematopoietic cells, as previously described (Liu et al., 2009).

Immunofluorescence and Confocal Microscopy

LKS cells or myeloid-restricted progenitors were sorted directly onto poly-L-lysine coated slides (Thermo Scientific). Cells were allowed to settle onto the slide for 20 minutes, fixed in methanol at RT for 10 minutes, washed once with PBS, and blocked with 30 mg/ml BSA/PBS at 37°C for 1 hour. Cells were stained with primary antibody in a humidified chamber at 4°C overnight.

For ANG/PABP localization, cells were stained with R163 rabbit polyclonal antibody (pAb) of ANG (10 μg/ml) and F-20 goat pAb of PABP (Santa Cruz #sc-18611, 1:50 dilution), followed with AF488-conjugated goat anti-rabbit (Thermo Scientific A11070, 1:600 dilution) and AF555-conjugated donkey anti-goat (Thermo Scientific A21432, 1:600 dilution). For RNH1/PABP localization, cells were stained with R127 rabbit pAb of RNH1 (5 μg/ml) and F-20 goat pAb of PABP followed with AF488-conjugated goat anti-rabbit AF488 and AF555-conjugated donkey anti-goat. For ANG/RNH1 localization, cells were stained with an in-house made mouse ANG-specific C527 monoclonal antibody (10 μg/ml) and R127 rabbit pAb of RNH1 (5 μg/ml), followed with AF488-conjugated rabbit anti-mouse (Thermo Scientific A11059, 1:600 dilution) and AF555-conjugated goat anti-rabbit (Thermo Scientific A21428, 1:600 dilution). Appropriate isotype controls were used at the same concentration. Images were acquired using Nikon A1R confocal microscopy.

Fluorescence Resonance Energy Transfer (FRET)

FRET was performed using the acceptor photo-bleaching method, as previously described (Pizzo et al., 2013). Briefly, AF488 was used as the donor and AF555 as the acceptors. Signals were photobleached to less than 10% of the initial fluorescent measurement. ROI measurements from LKS cells and myeloid-restricted progenitors were taken from 10 individual cells. FRET effiiency was calculated using the formula $E=(I_{DA}-I_D)/I_D$, where I_D and I_{DA} are fluorescence intensities before and after photobleaching, respectively. FRET was performed using Leica SP2 confocal microscopy.

Enzyme-linked Immunosorbent Assay (ELISA)

Mouse ANG serum levels were assessed by ELISA. Briefly, ELISA plates were coated overnight with 100 µl mouse ANG C527 (30 µg/ml in sodium carbonate/bicarbonate buffer, pH 8.5) and blocked with 300 µl BSA/PBS (5 mg/ml) for 1 hour at RT. 100 µl serum were plated and incubated overnight at RT, alongside a standard curve of mouse ANG protein with known amounts (30-30,720 ng/ml). The plate was washed 4 times with PBS-Tween (0.1%), 3 times with PBS, and incubated with 100 µl/well rabbit anti-angiogenin R163 (2 µg/ml) for 2 hours at RT. After washing, an alkaline phosphatase-labeled goat anti-rabbit IgG (1.25 µg/ml) was incubated for 1 hour at RT. The plates were again washed and 100 µl p-nitrophenyl phosphate (5 mg/ml, dissolved in 0.1 M diethanolamine containing 10 mM $MgCl_2$, pH 9.8) was added.

Supplementary Methods Table. Mouse qRT-PCR Primer Sequences

Gene	**Forward Primer (5' to 3')**	**Reverse Primer (5' to 3')**
Ang	AGCGAATGGAAGCCCTTACA	CTCATCGAAGTGGACAGGCA
p21	TGGAGTCAGGCGCAGATCCAC	CGCCATGAGCGCATCGCAATC
p27	AGGCAAACTCTGAGGACCGGCA	TGCTCCACAGTGCCAGCGTTC
p57	CGAGGAGCAGGACGAGAATC	GAAGAAGTCGTTCGCATTGGC
GATA3	GGTATCCTCCGACCCACCAC	CCAGCCAGGGCAGAGATCC
vWF	GGCGAGGATGGAGTTCGACA	TGACAGGGCTGATGGTCTGG
Bmi1	AAACCAGACCACTCCTGAACA	TCTTCTTCTCTTCATCTCATTTTTGA
Cyclin D1	GCGTACCCTGACACCAATCTCCTC	ACCTCCTCTTCGCACTTCTGCTCC
47S	TCCCGACTACTTCACTCCTG	CAAGAGAACACAACGAGCGAC
28S	CGCGACCTCAGATCAGACGT	GCTCTTCCCTGTTCACTCGC
a1	CCCTGGCTGAGCACTACCTT	CTGCATGCTTGGCTTGGA
Bcl2	TGGGATGCCTTTGTGGAACT	ACAGCCAGGAGAAATCAAACAG
Bcl-xl	GGCTGGGACACTTTTGTGGAT	GCGCTCCTGGCCTTTCC
Mcl1	CCCTCCCCCATCCTAATCAG	AGTAACAATGGAAAGCATGCCAAT
Bak	AATGGCATCTGGACAAGGAC	GTTCCTGCTGGTGGAGGTAA
Bax	TGGAGCTGCAGAGGATGATTG	AGCTGCCACCCGGAAGA
Bid	GAAGACGAGCTGCAGACAGATG	AATCTGGCTCTATTCTTCCTTGGTT
Bim	TTGGAGCTCTGCGGTCCTT	CAGCGGAGGTGGTGTGAAT
Noxa	GGAGTGCACCGGACATAACT	TTGAGCACACTCGTCCTTCA
Puma	GCGGCGGAGACAAGAAGA	AGTCCCATGAAGAGATTGTACATGAC
Rnh1	CGGTGCAAAGACATCAGCTCA	TCAAGCCGCAGTTCTGAAGG
β-Actin	GACGGCCAGGTCATCACTATTG	AGGAAGGCTGGAAAAGAGCC

Supplementary Methods Table. Human qRT-PCR Primer Sequences

Gene	**Forward Primer (5' to 3')**	**Reverse Primer (5' to 3')**
p21	GTCACTGTCTTGTACCCTTGTG	CGGCGTTTGGAGTGGTAGAAA
p27	TGCAACCGACGATTCTTCTACTCAA	CAAGCAGTGATGTATCTGATAAACAAGGA
p57	AGAGATCAGCGCCTGAGAAG	GGGCTCTTTGGGCTCTAAAC
GATA3	ACCACAACCACACTCTGGAGGA	TCGGTTTCTGGTCTGGATGCCT
vWF	CGGCTTGCACCATTCAGCTA	TGCAGAAGTGAGTATCACAGCCATC
Bmi1	AATCCCCACCTGATGTGTGT	GCTGGTCTCCAGGTAACGAA
Cyclin D1	AGCTCCTGTGCTGCGAAGTGGAAAC	AGTGTTCAATGAAATCGTGCGGGGT
β-Actin	AGCGAGCATCCCCCAAAGTT	GGGCACGAAGGCTCATCATT

Table S1. Cell counts for 8-12 week old *Ang*$^{-/-}$ mice, Related to Figure 1

Organ	Parameter	Unit	WT	*Ang*$^{-/-}$
Blood	WBC	x 10^3 / µl	8.60 ± 1.07	12.0 ± 1.18 *
	LYM	x 10^3 / µl	5.57 ± 0.89	8.90 ± 1.21 *
	MON	x 10^3 / µl	0.93 ± 0.30	0.80 ± 0.24
	NEU	x 10^3 / µl	2.10 ± 0.38	2.29 ± 0.39
	PLT	x 10^3 / µl	568 ± 80.2	665 ± 103
	$Mac1^+Gr1^+$	x 10^3 / µl	0.77 ± 0.08	0.53 ± 0.06 *
	$B220^+$	x 10^3 / µl	4.21 ± 0.54	6.36 ± 1.88 *
	$CD3e^+$	x 10^3 / µl	2.08 ± 0.34	2.74 ± 0.35
Bone Marrow	Cellularity	x 10^6 / femur	21.0 ± 0.65	20.2 ± 1.59
	$Mac1^+Gr1^+$	x 10^6 / femur	12.3 ± 0.65	9.78 ± 0.96 *
	$Ter119^+$	x 10^6 / femur	2.15 ± 0.35	2.03 ± 0.26
	$B220^+$	x 10^6 / femur	4.69 ± 0.31	6.23 ± 0.45 *
	$CD3e^+$	x 10^6 / femur	0.57 ± 0.04	0.58 ± 0.06

Data represent mean ± SEM.
*p<0.05
p-value relative to WT group
n=9

Table S2. Cell counts for 22 month old *Ang*$^{-/-}$ mice, Related to Figure 1

Organ	Parameter	Unit	WT	*Ang*$^{-/-}$
Blood	WBC	x 10^3 / µl	9.03 ± 1.72	4.67 ± 0.56 *
	LYM	x 10^3 / µl	6.89 ± 1.28	3.27 ± 0.64 *
	MON	x 10^3 / µl	0.22 ± 0.08	0.14 ± 0.02
	NEU	x 10^3 / µl	1.92 ± 0.55	1.26 ± 0.12
	PLT	x 10^3 / µl	960 ± 71.9	1038 ± 89.1
	$Mac1^+Gr1^+$	x 10^3 / µl	0.38 ± 0.07	0.17 ± 0.02 *
	$B220^+$	x 10^3 / µl	6.18 ± 1.34	2.63 ± 0.37 *
	$CD3e^+$	x 10^3 / µl	0.69 ± 0.13	0.60 ± 0.11
Bone Marrow	Cellularity	x 10^6 / femur	31.0 ± 1.17	27.3 ± 1.01 *
	$Mac1^+Gr1^+$	x 10^6 / femur	16.3 ± 0.77	12.6 ± 0.40 **
	$Ter119^+$	x 10^6 / femur	4.05 ± 0.44	2.73 ± 0.28 *
	$B220^+$	x 10^6 / femur	5.01 ± 0.35	3.03 ± 0.34 **
	$CD3e^+$	x 10^6 / femur	1.05 ± 0.14	0.49 ± 0.08 **

Data represent mean ± SEM.
*p<0.05, **p<0.01
p-value relative to WT group
n=5

Table S3. Cell counts for irradiated *Ang*$^{-/-}$ mice, Related to Figure 5

Cohort	Organ	Parameter	Unit		
				WT	***Ang*$^{-/-}$**
WT vs *Ang*$^{-/-}$	Bone Marrow	$Mac1^{+}Gr1^{+}$	10^6 / femur	2.79 ± 0.54	0.98 ± 0.19 *
		$Ter119^{+}$	10^6 / femur	1.22 ± 0.17	0.65 ± 0.10 *
		$B220^{+}$	10^6 / femur	2.15 ± 0.29	1.24 ± 0.28 *
		$CD3e^{+}$	10^6 / femur	0.22 ± 0.03	0.11 ± 0.02 *

Data represent mean ± SEM
*p<0.05
p-value relative to WT group
n=6
Dose: 4.0 Gy

Table S4. Cell counts for irradiated mice, Related to Figure 5

Cohort	Organ	Parameter	Unit				
				Untreated	**+ANG**	**4.0 Gy**	**4.0 Gy + ANG**
ANG Treatment Pre-Irradiation	Bone Marrow	LT-HSC	10^6 / femur	0.003 ± 0.001	0.002 ± 0.0003 *	0.001 ± 0.0003 **	0.003 ± 0.001
		ST-HSC	10^6 / femur	0.012 ± 0.002	0.007 ± 0.001 *	0.007 ± 0.001*	0.013 ± 0.002
		MPP	10^6 / femur	0.022 ± 0.003	0.014 ± 0.002 *	0.005 ± 0.001 ***	0.011 ± 0.002 *
		CLP	10^6 / femur	0.010 ± 0.002	0.004 ± 0.001 *	0.004 ± 0.001 *	0.007 ± 0.001
		pre-pro B	10^6 / femur	0.005 ± 0.001	0.003 ± 0.0005 *	0.001 ± 0.0003 **	0.004 ± 0.001
		CMP	10^6 / femur	0.139 ± 0.005	0.194 ± 0.024 *	0.072 ± 0.014 **	0.134 ± 0.024
		GMP	10^6 / femur	0.124 ± 0.006	0.172 ± 0.021*	0.063 ± 0.007 ***	0.126 ± 0.020
		MEP	10^6 / femur	0.123 ± 0.006	0.138 ± 0.012	0.017 ± 0.005 ***	0.063 ± 0.025
		$Mac1^+Gr1^+$	10^6 / femur	11.3 ± 0.65	11.2 ± 1.17	6.39 ± 1.13 **	10.7 ± 1.54
		$Ter119^+$	10^6 / femur	3.80 ± 0.17	3.49 ± 0.43	1.64 ± 0.38 ***	2.27 ± 0.55 *
		$B220^+$	10^6 / femur	6.04 ± 0.33	5.10 ± 0.72	3.26 ± 0.45 **	4.57 ± 0.65
		$CD3e^+$	10^6 / femur	0.58 ± 0.02	0.58 ± 0.17	0.36 ± 0.06 ***	0.62 ± 0.18
				Untreated	**+ANG**	**4.0 Gy**	**4.0 Gy + ANG**
ANG Treatment Post-Irradiation	Bone Marrow	LT-HSC	10^6 / femur	0.003 ± 0.0005	0.002 ± 0.0003 *	0.001 ± 0.0001***	0.002 ± 0.001
		ST-HSC	10^6 / femur	0.014 ± 0.001	0.009 ± 0.001 *	0.004 ± 0.0001***	0.009 ± 0.002
		MPP	10^6 / femur	0.021 ± 0.001	0.016 ± 0.002 *	0.005 ± 0.001 ***	0.014 ± 0.003
		CLP	10^6 / femur	0.006 ± 0.001	0.003 ± 0.001 *	0.002 ± 0.0001***	0.005 ± 0.001
		pre-pro B	10^6 / femur	0.006 ± 0.001	0.003 ± 0.001 *	0.001 ± 0.0002***	0.003 ± 0.001
		CMP	10^6 / femur	0.127 ± 0.010	0.190 ± 0.024 *	0.023 ± 0.003 ***	0.092 ± 0.019
		GMP	10^6 / femur	0.113 ± 0.014	0.181 ± 0.027 *	0.022 ± 0.002 ***	0.073 ± 0.018
		MEP	10^6 / femur	0.080 ± 0.025	0.121 ± 0.025	0.006 ± 0.001 *	0.052 ± 0.012
		$Mac1^+Gr1^+$	10^6 / femur	11.9 ± 0.44	11.0 ± 1.44	3.19 ± 0.23 ***	7.98 ± 1.92
		$Ter119^+$	10^6 / femur	2.99 ± 0.57	2.80 ± 0.44	0.78 ± 0.07 **	1.55 ± 0.41
		$B220^+$	10^6 / femur	5.68 ± 0.33	4.40 ± 0.63	2.17 ± 0.20 **	4.50 ± 1.14
		$CD3e^+$	10^6 / femur	0.54 ± 0.05	0.50 ± 0.16	0.28 ± 0.03 ***	0.41 ± 0.10

Data represent mean ± SEM
*p<0.05, **p<0.01, ***p<0.001
p-value relative to untreated group
n=6
Dose: 4.0 Gy
ANG Treatment: 1.25 mg/kg, three times daily as indicated

Table S5. Cell counts for lethally-irradiated mice with ANG pre-treatment, Related to Figure 5

Organ	Parameter	Unit	Day 0		Day 5		Day 10	
			Vehicle	+ANG	Vehicle	+ANG	Vehicle	+ANG
Blood	WBC	x 10^3 / µl	6.93 ± 0.89	6.76 ± 0.69	0.99 ± 0.36	3.50 ± 0.82 **	0.99 ± 0.59	4.23 ± 1.09 **
	LYM	x 10^3 / µl	4.99 ± 0.67	4.92 ± 0.46	0.54 ± 0.20	1.18 ± 0.28	0.57 ± 0.32	1.40 ± 0.36
	MON	x 10^3 / µl	0.47 ± 0.11	0.42 ± 0.08	0.03 ± 0.01	0.27 ± 0.06 **	0.09 ± 0.05	0.30 ± 0.08 *
	NEU	x 10^3 / µl	1.47 ± 0.29	1.44 ± 0.21	0.41 ± 0.15	2.05 ± 0.48 **	0.32 ± 0.21	2.53 ± 0.65 **
	PLT	x 10^3 / µl	826 ± 55	845 ± 69	243 ± 53	780 ± 97 ***	176 ± 57	555 ± 122 *
	$Mac1^+Gr1^+$	x 10^3 / µl	0.75 ± 0.09	0.75 ± 0.08	0.06 ± 0.02	0.48 ± 0.11 **	0.004 ± 0.001	0.83 ± 0.22 **
	$B220^+$	x 10^3 / µl	3.61 ± 0.448	3.55 ± 0.34	0.04 ± 0.01	0.72 ± 0.25 *	0.050 ± 0.039	0.88 ± 0.26 **
	$CD3e^+$	x 10^3 / µl	1.94 ± 0.25	1.88 ± 0.18	0.02 ± 0.01	1.49 ± 0.49 **	0.005 ± 0.004	1.73 ± 0.58 **

Data represent mean ± SEM
*p<0.05, **p<0.01, ***p<0.001
p-value relative to vehicle-treated group
n=10
Dose: 12.0 Gy
ANG Treatment: 1.25 mg/kg, three times daily pre-irradiation

Table S6. Cell Counts at 1 year post-transplant, Related to Figure 6

Organ	Parameter	Unit	0 ng/ml ANG	300 ng/ml ANG
Blood	WBC	x 10^3 / µl	9.55 ± 1.95	14.3 ± 0.90 *
	LYM	x 10^3 / µl	6.34 ± 1.49	10.9 ± 0.96 *
	MON	x 10^3 / µl	0.38 ± 0.02	0.38 ± 0.03
	NEU	x 10^3 / µl	2.55 ± 0.49	2.68 ± 0.25
	PLT	x 10^3 / µl	820 ± 132	1068 ± 93.1
	Total Donor	x 10^3 / µl	1.59 ± 1.24	7.43 ± 1.90 *
	$Mac1^+Gr1^+$	x 10^3 / µl	0.07 ± 0.05	0.25 ± 0.06 *
	$Mac1^{low}Gr1^{low}$	x 10^3 / µl	0.10 ± 0.06	0.10 ± 0.05
	$B220^+$	x 10^3 / µl	0.97 ± 0.81	4.81 ± 1.26 *
	$CD3e^+$	x 10^3 / µl	0.28 ± 0.22	1.45 ± 0.42 *

Data represent mean ± SEM.
*p<0.05
p-value relative to 0 ng/ml ANG group
n=6-7; mice from Figure 6C not used in secondary transplant, aged 1 year post-transplant

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