Supplementary methods:

Conventional Transmission Electron Microscopy

For conventional transmission electron microscopy, cells grown on a MatTek glass bottom dish were pre-fixed in a mixture of 2% glutaraldehyde and 2% paraformaldehyde in 0.1 M sodium cacodylate buffer, pH 7.2 (Electron Microscopy Sciences, Hatfield, PA, USA) overnight at 4°C, followed by post-fixation in a mixture of 1% osmium tetroxide and 1% potassium ferrocyanide in 0.1 M sodium cacodylate buffer for 15 minutes on ice. The fixed cells were en bloc contrasted with 1% uranyl acetate for 15 minutes at RT. Following contrasting, the cells were treated with Walton's lead aspartate for 8 minutes at 60°C. The fixed and contrasted cells were dehydrated in ascending ethanol series (10, 30, 50, 70, 80, 95, and 100 %), embedded in Spurr's resin (Electron Microscopy Sciences, Hatfield, PA, USA), and thermally polymerized for 24 hours at 70°C. The polymerized cells were transferred to resin by detaching a coverslip under the MatTek dish using liquid nitrogen. The resin polymerized cells were sectioned using a Leica EM ARTOS 3D ultramicrotome (Leica Microsystems, Deerfield, IL, USA) and a diamond knife (DiATOME, Hatfield, PA, USA). 70 nm ultrathin sections were obtained and observed with a Thermo Fisher Scientific Tecnai G2 F20 Twin transmission electron microscope (Thermo Fisher Scientific USA, Waltham, MA, USA) at 80 KeV with a 15 megapixel of AMT NanoSprint15 Mk-II high sensitivity sCMOS camera (Advanced Microscopy Techniques, Woburn, MA, USA).

Confocal Microscopy

MEG-01 cells were differentiated with PMA (100nM) in presence or absence of Ceefourin (20 µM) for 2 days in µ-Slide with 4 wells (ibidi), coated with fibronectin (Corning). Cells were stained with Wheat germ agglutinin (WGA, Invitrogen) and Hoechst 33342 dye (Thermo Fisher Scientific) 10 minutes before live imaging under confocal microscope (Zeiss Axio Observer with CSU-X spinning disc and 4 diode lasers) using 63X oil objective lens. Images were analyzed by SlideBook 6 software.

Co-immunoprecipitation

Differentiating MEG-01 cells were treated with or without Ceefourin2 were harvested after 2 days and lysed in M-PER mammalian protein extraction reagent (Pierce) with protease inhibitor cocktail (Roche) on ice for 30-45 minutes. Supernatant containing the protein was separated by centrifuging at maximum speed at 4°C for 15 minutes. Protein quantification was performed using BCA protein assay (Pierce). 250 µg of proteins from each treatment conditions were incubated with 3 µg of primary antibody (PKA-C, Bio-RAD, # VMA00679) or control Igg (G3A1 mAb IgG1 Isotype Control, Cell Signaling, #5415) overnight at 4°C. Lysis buffer was added to the protein-antibody mixture so that the concentration was 1 mg/ml. The mixture was incubated with protein G-agarose beads (Pierce) for 3 hours at 4°C and washed three times with the lysis buffer by spinning at 2000g, 4°C for 2 minutes. Co-immunoprecipitated proteins were eluted off the beads in Trident 6X Laemmli SDS sample buffer (Gene Tex, GTX16357) containing 25 mM dithiothreitol (DTT, Thermo Fisher) by shaking at 500 rpm, 37°C for 30 minutes. The supernatant containing the co-immunoprecipitated proteins were separated from the beads by centrifuging at 2000g, 4°C for 2 minutes and analyzed by immunoblotting.

Immunoblotting

Proteins were loaded into 4-15% gradient polyacrylamide gel and separated by SDS-PAGE gel electrophoresis. Proteins in the gel were transferred into nitrocellulose membrane, blocked with 5% non-fat dry milk for an hour at RT, probed with primary antibodies (ABCC4,clone M4I10, Abcam, # ab15602; GAPDH, Proteintech, 60004-1-IG; BAX, Cell Signaling, # 2772S; Bcl-XL, Cell signaling, # 2764S; Bcl-2, Cell signaling, # 3498S; PKA-C, Cell Signaling, # 4782S; PKA-RIIB, BD Transduction Lab, # 610626; Actin, clone AC-15, Sigma, # A1978; GATA1, Cell signaling, # 3535S; TPOR (MPL), BIOSS # bs-11311R; ETV6, Invitrogen, # PA5-109697) for overnight at 4°C. All the primary antibodies were used at 1:1000 dilution, except for GAPDH and Actin (1:10000). The membrane was washed three times with Tris-buffer saline containing Tween 20 before incubation in secondary antibodies (Peroxidase conjugated affinipure

Donkey Anti-Rat IgG (H+L), # 712-035-150; Donkey Anti-Rabbit IgG (H+L), #711-035-152; Donkey Anti-Mouse IgG (H+L), #715-035-150; Jackson Immuno Research Laboratories. Inc, 1:10000) for 1 hour at RT. The Bio-Rad Clarity TM western ECL chemiluminescence substrate was used for peroxidase detection, using Odyssey Fc imaging system (LI-COR Biosciences). The densitometric quantification of the immunoblots were performed using Image Studio Lite version 5.2.

Histochemistry

Bone marrow obtained from femur and tibia of mice were initially fixed in paraformaldehyde, dehydrated, and embedded in paraffin. The sections of paraffin-embedded tissues were stained with hematoxylin and eosin for morphological analysis. Hematoxylin stains nucleus blue and eosin stains extracellular matrix and cytoplasm pink, with other cellular structures taking different shades of pink. MKs were distinguished from other cells by their larger size, lobulated nucleus, and irregular edges with numerous villi. Fluorescence images were obtained using a Nikon Eclipse Ti fluorescence microscope with a 40X objective and analyzed by NIS Elements AR (version 4.5).

cAMP ELISA Assay

cAMP levels were quantified using Direct cAMP ELISA kit (Enzo), following the manufacturer's instructions.

siRNA transfection

MEG-01 cells were transfected with either negative control siRNA or ABCC4 siRNAs from Qiagen: Hs_ABCC4_3,5 and 8 Flexitube siRNA (#SI00081830, SI03096751, #SI04952136) using Lipofectamine 2000 as per the manufacturer's protocol. 25nM of siRNAs were complexed with 5µl of Lipofectamine 2000 in reduced serum media. The cells were incubated with ABCC4 siRNA-lipofectamine complex for overnight and treated with PMA (100nM). After incubation for another 48 hours, the cells were processed as needed.

ChIP-seq, ATAC-seq and Hi-C data analysis

964 The ChIP-seq from K562 cells were from ENCODE portal[61] with the following identifiers:
965 ENCFF783AFF, ENCFF484YEL, ENCFF072KHT, ENCFF533LHP, ENCFF204SDM,
966 ENCFF670JFE, ENCFF460URK and ENCFF832FFP. In brief, the single-end reads were
967 trimmed for adapters, aligned to hg19 and deduplicated using Picard; two replicates
968 were pooled, and fold change bigwig files were generated against INPUT.

969 The GMP and MEP ATAC-seq were from Corces, et.al[30] and UCSC Genome Browser
970 Track Hub URL - https://s3-us-west-1.amazonaws.com/chang-public-
971 data/2016_NatGen_ATAC-AML/hub.txt According to Corces, et.al, the reads were
972 aligned to hg19 using bowtie2, deduplicated by Picard and adjusted by quantile and GC
973 normalization using CQN R package.[62]

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975 Promoter capture Hi-C for $CD34^+$ hematopoietic progenitors cells were from Mifsud,
976 et.al[63], https://ftp.ebi.ac.uk/biostudies/fire/E-MTAB-/323/E-MTAB
977 2323/Files/TS5_CD34_promoter-other_significant_interactions.txt as per the authors'
978 description and data were preprocessed using HiCUP.

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