View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by IUPUIScholarWorks

HHS Public Access

Author manuscript

Curr Opin Hematol. Author manuscript; available in PMC 2018 September 24.

Published in final edited form as:

Curr Opin Hematol. 2018 July ; 25(4): 245–252. doi:10.1097/MOH.0000000000000429.

Enhancing human cord blood hematopoietic stem cell engraftment by targeting nuclear hormone receptors

Bin Guo, **Xinxin Huang**, and **Hal E. Broxmeyer**

Department of Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, Indiana, USA

Abstract

Purpose of review—Allogeneic hematopoietic cell transplantation (HCT) is a life-saving therapy for hematological and non-hematological diseases. Cord blood (CB) is a source of transplantable hematopoietic stem cells (HSCs), but limited numbers of HSCs in single CB units, which may cause delayed neutrophil, platelet, and immune cell reconstitution, is a major problem for efficient transplantation. *Ex vivo* expansion and enhanced homing of CB HSC may overcome this disadvantage and improve its long-term engraftment. Here, we discuss the role of nuclear hormone receptors (NRs) signaling in human CB HSC engraftment.

Recent findings—Antagonizing Retinoid acid receptor (RAR) signaling promotes human HSC expansion and increases myeloid cell production. CB $CD34^+$ cells expanded by SR1 promotes efficient myeloid recovery after transplantation compared with control groups, and leads to successful engraftment. Short-term treatment of glucocorticoids enhances homing and long-term engraftment of human HSCs and HPCs in NSG mice. PPARγ antagonism expands human HSCs and HPCs by preventing differentiation and enhancing glucose metabolism. These findings demonstrate that NR signaling components might be promising targets for improving human CB HCT.

Summary—Better understanding of molecular mechanisms underlying human HSC expansion and homing mediated by NR signaling pathways will facilitate enhanced HCT efficacy.

Keywords

Nuclear receptor; Human HSC; Expansion; Homing

INTRODUCTION

Homeostasis of hematopoiesis is maintained by intrinsic and extrinsic signals by hematopoietic stem (HSC) and progenitor (HPC) cells, rare immature cell populations residing in microenviromental niches [1–3]. HSC self-renew, or differentiate through HPC into all mature blood cells throughout [4]. Human HSC are major contributors for HCT

Correspondence to: Bin Guo, Ph.D., Department of Microbiology and Immunology, Indiana University School of Medicine, 950 West Walnut Street, R2-302, Indianapolis, IN 46202-5181 USA, Phone: 317-274-7568, Fax: 317-274-7592, binguo@iupui.edu.

Conflicts of interest
The authors have no conflicts of interest to declare.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[5,6]. Once infused into peripheral blood of recipients, HSC and HPC migrate and engraft in bone marrow (BM) niches, where a new hematopoietic system builds up [7,8]. Three major sources of HSC for HCT are: BM, peripheral blood and CB [9,10]. Compared with the other sources, CB has advantages, including ready availability, less strict HLA matching requirements, lower incidence of graft vs. host disease and virus infection, and low probability of relapse among patients with minimal residual disease [11–13]. However, delayed hematopoietic recovery and immune reconstitution due to limited numbers of HSCs are major limiting factors preventing the wider use of HCT based cell therapy. Progress to improve CB HSC engraftment and reconstitution includes mitigating effects of Extra Physiologic Oxygen Shock/Stress (EPHOSS) during cell collection [14], *ex vivo* expansion of HSC [15–17*] and enhancing HSC homing efficiency [18].

Nuclear hormone receptors (NR) are transcription factors which regulate expression of target genes by binding to specific response elements in the transcription units [19,20]. NR, consisting of 48 members in humans, are activated by steroid hormones such as glucocorticoids and estrogen, or non-steroid hormones such as retinoic acid, vitamin D, and thyroid hormones. NR members share a similar structure, composed of a highly variable A/B transactivation domain, a conserved DNA binding domain (C domain), a nuclear localization signal containing D domain and a relatively conserved ligand binding E domain [19,20]. Upon ligand binding, the conformation of NR changes and a repressor complex such as NCoR and SMRT corepressor disassociate from NR, followed by recruitment of transactivation complexes with histone acetyltransferase (HAT) activity and other transcription machinery, thus facilitating transcription of target genes[21]. NR are involved in physiological processes including: proliferation [22], differentiation [23,24], development [25] and metabolism [26,27]. To treat diseases caused by dysfunction of NR, synthetic agonists and antagonists of NR were developed to modulate its activity [28]. These diversified synthetic ligands help explore novel biological functions of NR in humans.

Here, we summarize recent progress regarding enhancing human HSC and HPC engraftment by modulating NR signaling.

RETINOID ACID SIGNALING AND HUMAN HSC EXPANSION

Retinoid acid receptor (RAR) serves as the nuclear receptor for all-trans retinoid acid (ATRA), the biologically active form of retinol (vitamin A) [29]. There are three different subtypes of RAR (α, β, γ), and each is alternatively spliced into at least two distinct isoforms [30]. Although RAR is highly conserved between mouse and human, functioning of RAR signaling in murine and human HSC homeostasis is quite different. *RARα* knockout mice show no abnormal phenotype of HSCs and HPCs, while HSC numbers are significantly reduced in *RARγ* knockout mouse BM [31]. BM HPC numbers are increased in *RARγ* knockout mice compared with wild type animals, suggesting that RARγ might regulate differentiation of their HSCs. Meanwhile, ATRA *ex vivo* treatment enhances repopulating capability of murine BM Lineage^{-}Sca-1^{+}c-Kit^{+} (LSK) cells, effects dependent on RARγ [31]. Physiological ATRA is derived from retinol, which is not synthesized by animals but is obtained from food (vegetables, fruits, animal livers) [32], so HSC homeostasis can be affected by availability of retinol in food. ATRA treatment protects

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

dormant HSCs from stress induced activation by restricting protein synthesis and reactive oxygen species (ROS) generation [33**]. Numbers of dormant HSCs in retinol free diet fed mice, in which the retinoid acid reservoir is depleted, is significantly reduced [33**].

RAR usually forms a heterodimer with retinoid X receptor (RXR) [34]. RXRα signaling negatively regulates granulocyte development from HSCs and HPCs in humans and mice [35], while in vivo hematopoiesis in RXRα knock out mice is normal [36]. Since there are two other isoforms of RXR (RXRβ, RXRγ) [30], normal hematopoiesis of RXRα knock out mice might be due to functional redundancy of different isoforms. It would be interesting to explore roles of RXR signaling in HSC self-renewal and maintenance using distinct RXR isoform double or triple knock out mice, since little is known of RXR in mouse and human HSC homeostasis.

Although activation of RAR signaling positively regulates development and function of mouse embryonic and adult HSC [31, 37, 38], human CB HSC self-renewal appears negatively modulated by the RAR pathway. Aldehyde dehydrogenase (ALDH) is a key enzyme in the RA synthesis pathway *in vivo*, and is characterized as a marker of HSCs and other tissue stem cells [39–41]. There are many ALDH isoforms. ALDH1 is considered the major isoform in HSCs and HPCs [42,43]. Treatment of human BM and CB $CD34^{+}CD38^{-}$ cells with diethylaminobenzaldehyde (DEAB), an ALDH inhibitor, enhances expansion and maintenance of HSCs and HPCs, as well as the *in vivo* frequency of SCID-repopulating cells (SRCs) in immune-compromised NOD/SCID mice [43]. Enhanced expansion of HSCs by DEAB can be reversed by RA induced differentiation [43]. Although HSCs themselves have the capability to convert retinol to RA [44], it would be interesting to determine whether inhibition of ALDH in HSCs or HPCs leads to down-regulation of RA signaling, and thus stimulates human HSC expansion and maintenance. BM stromal cells secrete CYP26 in the serum to inactivate and prevent RA signaling, and thus regulate human HSC self-renewal [45], suggesting that modulating RA signaling by targeting microenviromental niches represents a promising way to enhance *ex vivo* human HSC expansion. Treatment of $CD34^{+}CD38^{-}$ cells with LG1506, a selective RXR modulator, enhances human HSC and HPC expansion and long-term engraftment in NOD/SCID mice [46]. Mechanistically, once binding with LG1506, the RXR-RAR complex recruits silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) corepressors to promoters of target genes such as *CD38*, thus inhibiting differentiation of HSCs [46]. Recently, it was found that RARα antagonist increases myeloid cell production and promotes expansion of human HSCs, while RARγ antagonist had no effect due to different sensitivity to ATRA [47]. RXR forms heterodimers with other NRs, including liver X receptor (LXR), thyroid hormone receptor (THR), vitamin D receptor (VDR), peroxisome proliferator-activated receptors (PPARs). Future studies should characterize roles of these RXR heterodimers in human HSC maintenance and engraftment.

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

GLUCOCORTICOID SIGNALING IN HOMING AND ENGRAFTMENT OF HUMAN HSCS

Glucocorticoid (GC) receptor (GR) is a member of the steroid nuclear hormone receptor subfamily, which also includes mineralocorticoid receptor (MR), estrogen receptor (ER), androgen receptor (AR), and progestogen receptor (PR) [19]. Unliganded GR resides in the cytoplasm and is complexed with HSP90 and HSP70 [48]. Upon binding with GC, GR translocates into the nucleus and binds to GC response elements (GREs) in transcription units of target genes [49]. Co-activators such as SRC-1and CBP/p300 are recruited by activated GR, thus facilitating transcription of target genes [49]. GC/GR signaling is involved in many physiological processes, including carbohydrate metabolism, energy homeostasis, development and immune function [48]. GC levels are controlled by hypothalamic-pituitary-adrenal (HPA) axis *in vivo* [48]. In mouse and rat, the major endogenous GC is corticosterone, while in primates including humans the endogenous active GC is cortisol (or hydrocortisone) [50]. There are many synthetic GCs, such as dexamethasone, prednisone and fluticasone, which have been widely used as FDA approved drugs for anti-inflammation, allergy or asthma [48,51].

GCs regulate erythropoiesis. Co-culture with GCs *in vitro* promotes proliferation of erythroid progenitors [52]; *in vivo*, GR signaling is essential for stress-induced expansion of erythroid progenitors [52]. GR synergizes with PPARα promoting self-renewal of erythroid progenitor cells [53]. GC/GR signaling also plays pivotal roles in HSC homeostasis, including HSC production, HSC mobilization and HSC homing. During embryonic zebrafish hematopoiesis, serotonin regulates formation of HSCs and HPCs via HPA axis-mediated GR activation [54*]. Upon developmental hypoxic stress, HIF-1α is activated and induces neuronal serotonin synthesis to regulate cortisol-dependent production of HSCs and HPCs [54*]. Whether HPA-GR mediated HSC and HPC production is conserved in adults, needs further study. The central nervous system not only regulates HSC formation, but also regulates HSC mobilization via the HPA axis. HPA-GR signaling induced by muscarinic receptor type-1 (Chrm1) in hypothalamus is essential for G-CSF induced HSC and HPC mobilization [55*]. Mechanistically, physiological concentrations of GCs promote migration of HSCs and HPCs by modulating actin polymerization and microtubule assembly [55*]. However, administration of high dose GCs significantly suppresses egress of HSCs and HPCs mobilized by G-CSF [55*]. It is unknown if this GCs dependent mobilization of G-CSF is conserved in humans. Interestingly, GR is highly expressed in human CB $CD34^+$ HSCs and HPCs, suggesting that GC/GR signaling might play a role in human HSC physiological function [56**]. In a compound screen to search for chemical candidates which enhance human HSC and HPC homing, dexamethasone was identified as a significant enhancer of *CXCR4* expression and SDF1/CXCR4 axis-mediated chemotaxis [56**]. Short-term pretreatment of CB $CD34^+$ cells with other synthetic GCs including Flonase (fluticasone propionate), cortisol (hydrocortisone), and Medrol (methylprednisolone) promoted *CXCR4* expression and chemotaxis of HSCs and HPCs [56**]. Flonase pretreated CB $CD34^+$ cells manifested significantly enhanced SRCs, and enhanced human cell chimerism in primary and secondary recipient NSG mice, demonstrating effects of GCs on long-term repopulating, self-renewing HSC in CB cells [56**]. Upon GCs treatment,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

cytoplasmic GR in CB HSCs and HPCs was activated. Activated GR translocated into the nucleus and bound to GREs in the human *CXCR4* transcription unit (Fig. 1). SRC1/p300 histone acetyltransferase complex was recruited to promote histone H4 acetylation associated with *CXCR4*, thus facilitating transcription and expression of *CXCR4* in CB HSCs and HPCs. Unexpectedly, CBP was not involved in this process although in most case p300 and CBP function as a complex, further suggesting cell type and context specific effects of GC signaling. There are two isoforms of *CXCR4 (CXCR4-A* and *CXCR4-B)* in human cells due to alternative splicing. The promoters of *CXCR4-A* and *CXCR4-B* are totally different. The GRE locates in the promoter of *CXCR4-A* and the first intron of *CXCR4-B*. Since mRNA levels of *CXCR4-A* and *CXCR4-B* are significantly upregulated (our unpublished data), it would be interesting to know if there are functional differences between these two human *CXCR4* isoforms in migration and homing of HSCs and HPCs. There is no GRE throughout the mouse *Cxcr4* transcription unit, and *Cxcr4* expression and SDF-1 induced chemotaxis of mouse BM HSCs and HPCs remain unchanged upon GC treatment [56**]. Whether GC pretreatment of mouse BM HSCs and HPCs enhances their homing and engraftment by mechanisms independent of the SDF-1/CXCR4 axis needs investigation.

ANTAGONIZING PPARγ SIGNALING EXPANDS HUMAN HSCS

The peroxisome proliferator-activated receptors (PPARs) family consists of three subtypes, PPARα, δ/β and γ. They are ligand-dependent transcription factors regulating genes involved in energy metabolism [57]. PPARα is highly expressed in liver and other tissues/cells with a high fatty acid oxidation (FAO) rate, and mainly regulates lipid and lipoprotein metabolism [57]. Of interest, PPARα activation promotes expansion and self-renewal of erythroid progenitors [53]. Whether this process is dependent on FAO remains unknown. PPARδ is mainly involved in FAO in skeletal and cardiac muscles [57]. PPARδ dependent FAO regulates asymmetric division of mouse HSC, and thus is essential for HSC maintenance [58]. PPARγ is mainly expressed, but not restricted, in adipose tissue, and mediates transcription of genes involved in adipogenesis, lipid metabolism and glucose homeostasis [59].

In a compound screen, we found that PPARγ antagonist GW9662 significantly promotes *ex vivo* expansion of human CB HSCs and HPCs in RPMI1640 medium containing 10% fetal bovine serum (FBS) and cytokines (TPO, SCF, FLT-3L) [60**]. *PPARγ* is highly expressed in human CB HSCs, and knockdown of *PPARγ* in CB $CD34^+$ cells enhances *ex vivo* expansion of HSCs, suggesting that PPARγ signaling functions as a negative regulator of human HSC self-renewal [60**]. Mechanistically, antagonizing PPARγ down-regulates differentiation associated genes, including *CD38*, *CD1d*, *HIC1*, *FAM20C*, *DUSP4*, *DHRS3* and *ALDH1A2*, and a negative regulator of glycolysis, *FBP1*[60**]. It has been shown that inhibition of ALDH1A2 significantly promotes expansion and maintenance of CB HSCs [43], which demonstrates that antagonizing PPARγ expansion of CB HSCs may act in part by preventing RA-induced differentiation. Importantly, PPARγ antagonism promotes glycolysis of CB HSCs and HPCs, while it has no effect on mitochondria metabolism [60**]. Loss of function of FBP1 was sufficient to expand CB HSCs and HPCs which was dependent on glucose metabolism. Antagonizing PPARγ-FBP1 signaling had no effect on

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

expansion and glucose metabolism of CB HSCs and HPCs when CD34$^+$ cells were cultured in StemSpan™ Serum-Free Expansion Medium II (SFEM II) (our unpublished data). Interestingly, expression of PPARγ and FBP1 is greatly downregulated, while glycolysis is significantly enhanced when CD34$^+$ cells are *ex vivo* cultured in SFEM II compared with 10% FBS containing RPMI1640 regular medium (our unpublished data), suggesting that PPARγ-FBP1 signaling is repressed by unknown ingredients in SFEM II. These findings indicate that the PPARγ-FBP1 axis might function as a metabolic switch for expansion and self-renewal of CB HSCs and HPCs (Fig. 2).

Inhibition of FBP1 enhances glucose metabolism in many types of cancer cells, while overexpression of *FBP1* suppresses growth of cancer cells by compromising glycolysis [61,62]. It is unknown if leukemia cell growth is dependent on glucose metabolism activated by suppressing FBP1, and if inhibition of FBP1 impairs mitochondria metabolism in leukemia. PPARγ agonist glitazones decreases expression of STAT5 target genes, *HIF2α* and *CITED2*, and disrupts quiescence and stemness of chronic myeloid leukaemia (CML) stem cells LSCs [63]. Further studies are needed to determine if PPARγ activation impairs glucose metabolism by increasing *FBP1* expression in CML LSCs. In primates infected by human and simian immunodeficiency viruses, the multipotent potential of their HPCs is disrupted, which is dependent on repression of *STAT5* by ectopic activation of PPARγ [64]. Whether STAT5 signaling is involved in expansion of CB HSCs and HPCs by antagonizing PPARγ needs study. Knockdown of *PPARγ* in Fancd2 deficient murine HSCs significantly enhances their repopulating capability in recipient mice, while loss of function of PPARγ in wild type murine HSCs has no significant change on their engraftment [65*]. PPARγ antagonism has no effect on expansion of mouse BM HSCs and HPCs, and doesn't downregulate expression of differentiation associated genes and *Fbp1* in mouse BM lineage negative cells [60**]. PPARγ and its co-activators are upregulated in human *FANCD2*-deficient lymphoblastic cell lines and primary Fanconi patient samples [65*]. Future studies should determine the possible role of FBP1-mediated glucose metabolism and mitochondria metabolism in *FANCD2*-deficient HSCs.

CONCLUSION

Transcriptional regulation is one key intrinsic mechanism underlying human HSC expansion and self-renewal. As important members of transcription factors, NRs including RAR, GR and PPARγ play significant roles in expansion, self-renewal, homing and engraftment of human CB HSCs. Sufficient HSC numbers and efficient HSC homing are pivotal for successful clinical CB HCT, especially in adults. The more we know about molecular mechanisms of CB HSC self-renewal and homing, the better efficacy we can achieve in CB HCT clinical trials. Overexpression of *Musashi-2* (*MSI2*), encoding an RNA binding protein, significantly promotes expansion of CB HSCs by suppressing aryl hydrocarbon receptor (AhR) signaling [66*]. Simultaneous transplantation of an SR1 (AhR antagonist) expanded CB-derived CD34$^+$ cell population and an unmanipulated CB unit significantly promoted faster recovery of neutrophils and platelets after infusion [17*]. It would be of interest to determine the efficacy of combining SR1 with NR ligands, especially the homing enhancer Flonase in CB HCT. Recently, transplantable human HSCs have been successfully reprogrammed from iPS and endothelial cells [67,68**]. Can engraftment of these

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

reprogrammed HSCs be enhanced by modulating NR signaling? Since many NR ligands are FDA approved drugs, NRs represent promising targets for enhancing engraftment of human CB HCT.

Acknowledgements

None.

Financial support and sponsorship

The work was supported by US Public Health Service Grants from the NIH to HEB: (R01 HL112669, R01 HL056416, U54 DK106846).

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

1. Doulatov S, Notta F, Laurenti E, Dick JE. Hematopoiesis: a human perspective. Cell Stem Cell 2012; 10:120–136. [PubMed: 22305562]
2. Morrison SJ, Scadden DT. The bone marrow niche for haematopoietic stem cells. Nature 2014; 505:327–334. [PubMed: 24429631]
3. Eaves CJ. Hematopoietic stem cells: concepts, definitions, and the new reality. Blood 2015; 125:2605–2613. [PubMed: 25762175]
4. Orkin SH, Zon LI. Hematopoiesis: an evolving paradigm for stem cell biology. Cell 2008; 132:631–644. [PubMed: 18295580]
5. Notta F, Doulatov S, Laurenti E, et al. Isolation of single human hematopoietic stem cells capable of long-term multilineage engraftment. Science 2011; 333:218–221. [PubMed: 21737740]
6. Vedi A, Santoro A, Dunant CF, et al. Molecular landscapes of human hematopoietic stem cells in health and leukemia. Ann N Y Acad Sci 2016; 1370:5–14. [PubMed: 26663266]
7. Lapidot T, Dar A, Kollet O. How do stem cells find their way home? Blood 2005; 106:1901–1910. [PubMed: 15890683]
8. Ratajczak MZ, Suszynska M. Emerging Strategies to Enhance Homing and Engraftment of Hematopoietic Stem Cells. Stem Cell Rev 2016; 12:121–128. [PubMed: 26400757]
9. Sirinoglu Demiriz I, Tekgunduz E, Altuntas F. What is the most appropriate source for hematopoietic stem cell transplantation? Peripheral stem cell/bone marrow/cord blood. Bone Marrow Res 2012; 2012:834040. [PubMed: 23056949]
10. Ballen KK, Gluckman E, Broxmeyer HE. Umbilical cord blood transplantation: the first 25 years and beyond. Blood 2013; 122:491–498. [PubMed: 23673863]
11. Broxmeyer HE, Farag S. Background and future considerations for human cord blood hematopoietic cell transplantation, including economic concerns. Stem Cells Dev 2013; 22:103–110. [PubMed: 24304086]
12. Broxmeyer HE. Enhancing the efficacy of engraftment of cord blood for hematopoietic cell transplantation. Transfus Apher Sci 2016; 54:364–372. [PubMed: 27211041]
13. Milano F, Gooley T, Wood B, et al. Cord-Blood Transplantation in Patients with Minimal Residual Disease. N Engl J Med 2016; 375:944–953. [PubMed: 27602666]
14. Mantel CR, O'Leary HA, Chitteti BR, et al. Enhancing Hematopoietic Stem Cell Transplantation Efficacy by Mitigating Oxygen Shock. Cell 2015; 161:1553–1565. [PubMed: 26073944]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

15. Boitano AE, Wang J, Romeo R, et al. Aryl hydrocarbon receptor antagonists promote the expansion of human hematopoietic stem cells. Science 2010; 329:1345–1348. [PubMed: 20688981]
16. Fares I, Chagraoui J, Gareau Y, et al. Pyrimidoindole derivatives are agonists of human hematopoietic stem cell self-renewal. Science 2014; 345:1509–1512. [PubMed: 25237102]
17. Wagner JE, Jr, Brunstein CG, Boitano AE, et al. Phase I/II Trial of StemRegenin-1 Expanded Umbilical Cord Blood Hematopoietic Stem Cells Supports Testing as a Stand-Alone Graft. Cell Stem Cell 2016; 18:144–155. [PubMed: 26669897] * This is the first Phase I/II clinical study to demonstrate that *ex vivo* expanded CB HSCs/HPCs by SR1 show significant faster recovery of neutrophils and platelets in patients.
18. Ratajczak MZ, Suszynska M. Emerging Strategies to Enhance Homing and Engraftment of Hematopoietic Stem Cells. Stem Cell Rev 2016; 12:121–128. [PubMed: 26400757]
19. Sever R, Glass CK. Signaling by Nuclear Receptors. Cold Spring Harb Perspect Biol 2013; 5:a016709. [PubMed: 23457262]
20. Evans RM, Mangelsdorf DJ. Nuclear Receptors, RXR, and the Big Bang. Cell 2014; 157:255–266. [PubMed: 24679540]
21. Young JC, Hartl FU. Chaperones and transcriptional regulation by nuclear receptors. Nature Structural Biology 2002; 9:640–642. [PubMed: 12198482]
22. Sirin O, Lukov GL, Mao R, et al. The orphan nuclear receptor Nurr1 restricts the proliferation of haematopoietic stem cells. Nat Cell Biol 2010; 12:1213–1219. [PubMed: 21076412]
23. Jeong Y, Mangelsdorf DJ. Nuclear receptor regulation of stemness and stem cell differentiation. Experimental & Molecular Medicine 2009; 41:525–537. [PubMed: 19696553]
24. Castelo-Branco G, Lilja T, Wallenborg K, et al. Neural stem cell differentiation is dictated by distinct actions of nuclear receptor corepressors and histone deacetylases. Stem Cell Reports 2014; 3:502–515. [PubMed: 25241747]
25. Schneider C, Nobs SP, Kurrer M, et al. Induction of the nuclear receptor PPAR-γ by the cytokine GM-CSF is critical for the differentiation of fetal monocytes into alveolar macrophages. Nat Immunol 2014; 15:1026–37. [PubMed: 25263125]
26. Ahmadian M, Suh JM, Hah N, et al. PPARγ signaling and metabolism: the good, the bad and the future. Nat Med 2013; 19:557–566. [PubMed: 23652116]
27. Bovenga F, Sabbà C, Moschetta A. Uncoupling nuclear receptor LXR and cholesterol metabolism in cancer. Cell Metab 2015; 21:517–526. [PubMed: 25863245]
28. Burris TP, Solt LA, Wang Y, et al. Nuclear Receptors and Their Selective Pharmacologic Modulators. Pharmacol Rev 2013; 65:710–778. [PubMed: 23457206]
29. Allenby G, Bocquel MT, Saunders M, et al. Retinoic acid receptors and retinoid X receptors: interactions with endogenous retinoic acids. Proc Natl Acad Sci U S A 1993; 9030–34.
30. Al Tanoury Z, Piskunov A, Rochette-Egly C. Vitamin A and retinoid signaling: genomic and nongenomic effects. J Lipid Res 2013; 54:1761–1775. [PubMed: 23440512]
31. Purton LE, Dworkin S, Olsen GH, et al. RARgamma is critical for maintaining a balance between hematopoietic stem cell self-renewal and differentiation. J Exp Med 2006; 203:1283–1293. [PubMed: 16682494]
32. Brossaud J, Pallet V, Corcuff JB. Vitamin A, endocrine tissues and hormones: interplay and interactions. Endocr Connect 2017; pii: EC-17–0101. doi: 10.1530/EC-17-0101.
33. Cabezas-Wallscheid N, Buettner F, Sommerkamp P, et al. Vitamin A-Retinoic Acid Signaling Regulates Hematopoietic Stem Cell Dormancy. Cell 2017; 169:807–823. [PubMed: 28479188] ** This study demonstrates that vitamin A-retionic acid signaling maintains HSC stemness and quiescence *in vivo*, and for the first time suggests that vitamin A free or low diet might impair HSC dormancy.
34. Altucci L, Leibowitz MD, Ogilvie KM, et al. RAR and RXR modulation in cancer and metabolic disease. Nat Rev Drug Discov 2007; 6:793–810. [PubMed: 17906642]
35. Taschner S, Koesters C, Platzer B, et al. Down-regulation of RXRalpha expression is essential for neutrophil development from granulocyte/monocyte progenitors. Blood 2007; 109:971–979. [PubMed: 17018855]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

36. Ricote M, Snyder CS, Leung HY, et al. Normal hematopoiesis after conditional targeting of RXRalpha in murine hematopoietic stem/progenitor cells. J Leukoc Biol 2006; 80:850–861. [PubMed: 16888087]
37. Purton LE, Bernstein ID, Collins SJ. All-trans retinoic acid enhances the long-term repopulating activity of cultured hematopoietic stem cells. Blood 2000; 95:470–477. [PubMed: 10627451]
38. Chanda B, Ditadi A, Iscove NN, Keller G. Retinoic acid signaling is essential for embryonic hematopoietic stem cell development. Cell 2013; 155:215–227. [PubMed: 24074870]
39. Lioznov MV, Freiberger P, Kröger N, et al. Aldehyde dehydrogenase activity as a marker for the quality of hematopoietic stem cell transplants. Bone Marrow Transplant 2005; 35:909–914. [PubMed: 15765109]
40. Moreb JS. Aldehyde dehydrogenase as a marker for stem cells. Curr Stem Cell Res Ther 2008; 3:237–246. [PubMed: 19075754]
41. Marcato P, Dean CA, Giacomantonio CA, Lee PW. Aldehyde dehydrogenase: its role as a cancer stem cell marker comes down to the specific isoform. Cell Cycle 2011; 10:1378–1384. [PubMed: 21552008]
42. Kastan MB, Schlaffer E, Russo JE et al. Direct demonstration of elevated aldehyde dehydrogenase in human hematopoietic progenitor cells. Blood 1990; 75:1947–1950. [PubMed: 2337669]
43. Chute JP, Muramoto GG, Whitesides J, et al. Inhibition of aldehyde dehydrogenase and retinoid signaling induces the expansion of human hematopoietic stem cells. Proc Natl Acad Sci U S A 2006; 103:11707–11712. [PubMed: 16857736]
44. Purton LE. Roles of retinoids and retinoic Acid receptors in the regulation of hematopoietic stem cell self-renewal and differentiation. PPAR Res 2007; 2007:87934. [PubMed: 17846663]
45. Ghiaur G, Yegnasubramanian S, Perkins B, et al. Regulation of human hematopoietic stem cell self-renewal by the microenvironment's control of retinoic acid signaling. Proc Natl Acad Sci U S A 2013; 110:16121–16126. [PubMed: 24043786]
46. Safi R, Muramoto GG, Salter AB, et al. Pharmacological manipulation of the RAR/RXR signaling pathway maintains the repopulating capacity of hematopoietic stem cells in culture. Mol Endocrinol 2009; 23:188–201. [PubMed: 19106195]
47. Brown G, Marchwicka A, Cunningham A, et al. Antagonizing Retinoic Acid Receptors Increases Myeloid Cell Production by Cultured Human Hematopoietic Stem Cells. Arch Immunol Ther Exp (Warsz) 2017; 65:69–81. [PubMed: 27412076]
48. Kadmiel M, Cidlowski JA. Glucocorticoid receptor signaling in health and disease. Trends Pharmacol Sci 2013; 34:518–530. [PubMed: 23953592]
49. Weikum ER, Knuesel MT, Ortlund EA, Yamamoto KR. Glucocorticoid receptor control of transcription: precision and plasticity via allostery. Nat Rev Mol Cell Biol 2017; 18:159–174. [PubMed: 28053348]
50. Goosens KA, Sapolsky RM. Stress and Glucocorticoid Contributions to Normal and Pathological Aging In: Riddle DR, editor. SourceBrain Aging: Models, Methods, and Mechanisms. Boca Raton (FL): CRC Press/Taylor & Francis; 2007 Chapter 13. Frontiers in Neuroscience.
51. Holgate ST, Polosa R. Treatment strategies for allergy and asthma. Nat Rev Immunol 2008; 8:218–230. [PubMed: 18274559]
52. Bauer A, Tronche F, Wessely O, et al. The glucocorticoid receptor is required for stress erythropoiesis. Genes Dev 1999; 13:2996–3002. [PubMed: 10580006]
53. Lee HY, Gao X, Barrasa MI, et al. PPAR-α and glucocorticoid receptor synergize to promote erythroid progenitor self-renewal. Nature 2015; 522:474–477. [PubMed: 25970251]
54. Kwan W, Cortes M, Frost I, et al. The Central Nervous System Regulates Embryonic HSPC Production via Stress-Responsive Glucocorticoid Receptor Signaling. Cell Stem Cell 2016; 19:370–382. [PubMed: 27424782] * This study demonstrates that the central nervous system controls embryonic HSC and HPC production by glucocorticoid signaling.
55. Pierce H, Zhang D, Magnon C, et al. Cholinergic Signals from the CNS Regulate G-CSF-Mediated HSC Mobilization from Bone Marrow via a Glucocorticoid Signaling Relay. Cell Stem Cell 2017; 20:648–658. [PubMed: 28196601] * This paper shows that the central nervous system regulates HSC mobilization via glucocorticoid signaling.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

56. Guo B, Huang X, Cooper S, Broxmeyer HE. Glucocorticoid hormone-induced chromatin remodeling enhances human hematopoietic stem cell homing and engraftment. Nat Med 2017; 23:424–428. [PubMed: 28263313] ** This paper shows that glucocorticoid signaling functions as an activator of *CXCR4* transcription in CB HSCs/HPCs, and suggests that glucocorticoids might be used as potential drugs to enhance clinical efficacy of HCT.
57. Wang YX. PPARs: diverse regulators in energy metabolism and metabolic diseases. Cell Res 2010; 20:124–137. [PubMed: 20101262]
58. Ito K, Carracedo A, Weiss D, et al. A PML–PPAR-δ pathway for fatty acid oxidation regulates hematopoietic stem cell maintenance. Nat Med 2012; 18:1350–1358. [PubMed: 22902876]
59. Ahmadian M, Suh JM, Hah N, et al. PPARγ signaling and metabolism: the good, the bad and the future. Nat Med 2013; 19:557–566. [PubMed: 23652116]
60. Guo B, Huang X, Lee MR, Lee SA, Broxmeyer HE. Antagonizing PPARγ-FBP1 axis repressed glycolysis expands human hematopoietic stem and progenitor cells. Nat Med 2017.** This study identifies PPARγ-FBP1 axis as a negative regulator of human HSC/HPC maintenance, expansion and glucose metabolism.
61. Dong C, Yuan T, Wu Y, et al. Loss of FBP1 by Snail-mediated repression provides metabolic advantages in basal-like breast cancer. Cancer Cell 2013; 23:316–331. [PubMed: 23453623]
62. Li B, Qiu B, Lee DS, et al. Fructose-1,6-bisphosphatase opposes renal carcinoma progression. Nature 2014; 513:251–255. [PubMed: 25043030]
63. Prost S, Relouzat F, Spentchian M, et al. Erosion of the chronic myeloid leukaemia stem cell pool by PPARγ agonists. Nature 2015; 525:380–383. [PubMed: 26331539]
64. Prost S, Le Dantec M, Augé S, et al. Human and simian immunodeficiency viruses deregulate early hematopoiesis through a Nef/PPARgamma/STAT5 signaling pathway in macaques. J Clin Invest 2008; 118:1765–1775. [PubMed: 18431514]
65. Sertorio M, Du W, Amarachintha S, et al. In Vivo RNAi Screen Unveils PPARγ as a Regulator of Hematopoietic Stem Cell Homeostasis. Stem Cell Reports 2017; 8:1242–1255. [PubMed: 28416286] * This paper shows that PPARγ signaling is ectopically activated in Fanconi anemia patient samples, and knockdown of PPARγ enhances reconstutiting capability of FANCD2-deficient HSCs.
66. Rentas S, Holzapfel N, Belew MS, et al. Musashi-2 attenuates AHR signalling to expand human haematopoietic stem cells. Nature 2016; 532:508–511. [PubMed: 27121842] * This study shows that Musashi-2, a RNA binding protein, regulates human HSC expansion by attenuating AHR signaling.
67. Sandler VM, Lis R, Liu Y, et al. Reprogramming human endothelial cells to haematopoietic cells requires vascular induction. Nature 2014; 511:312–8. [PubMed: 25030167]
68. Sugimura R, Jha DK, Han A, et al. Haematopoietic stem and progenitor cells from human pluripotent stem cells. Nature 2017; 545:432–438. [PubMed: 28514439] ** This is the first study to demonstrate that transplantable human HSCs can be reprogrammed from human pluripotent stem cells.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

KEY POINTS

- Antagonizing RAR signaling increases myeloid cell production and promotes human HSC expansion and engraftment by inhibiting differentiation.
- Attenuating AhR signaling enhances human HSC expansion, and SR1 expanded HSCs and HPCs show significant faster recovery of neutrophils and platelets in clinical study of HCT.
- Glucocorticoid pretreatment of human HSCs and HPCs enhances their homing and engraftment capability in NSG mice.
- PPARγ antagonism promotes self-renewal and engraftment of human HSCs and HPCs by switching on FBP1-repressed glucose metabolism and preventing differentiation. PPARγ is ectopically activated in primary fanconi patient samples, and PPARγ signaling might be an effective target in therapy of fanconi patients.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

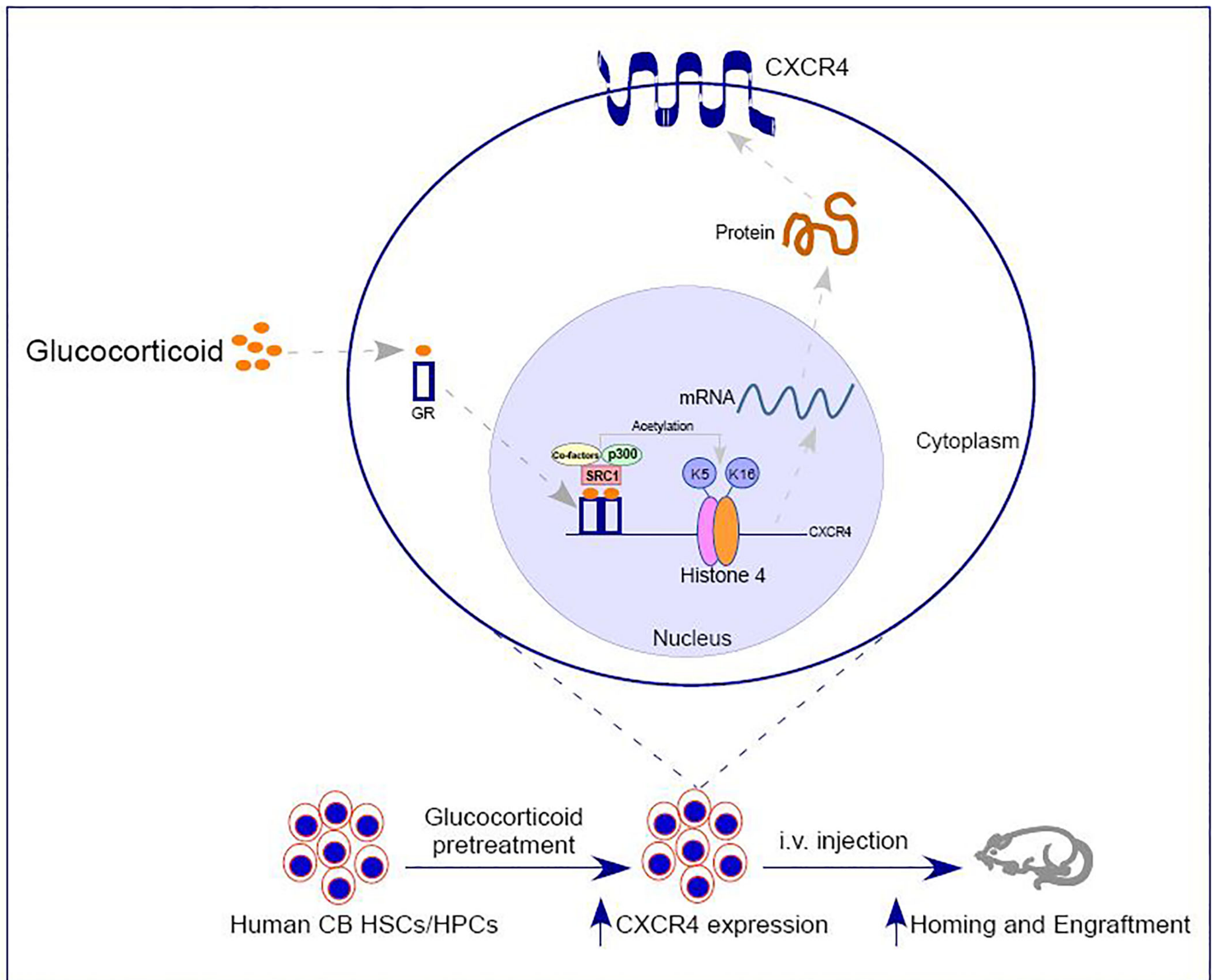

FIGURE 1.

Glucocorticoid (GC) pretreatment enhances homing and engraftment of human CB HSCs/HPCs by transcriptionally increasing *CXCR4* expression. GC activates glucocorticoid receptor in the cytoplasm, and GC-GR complex translocates into the nucleus and binds as a dimer to the GC response element in *CXCR4* transcription unit. SRC1-p300 histone acetyltransferase complex is recruited to enhance histone H4 (H4K5 and H4K16) acetylation, thus facilitating transcription of CXCR4 in CB HSCs/HPCs [56**].

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

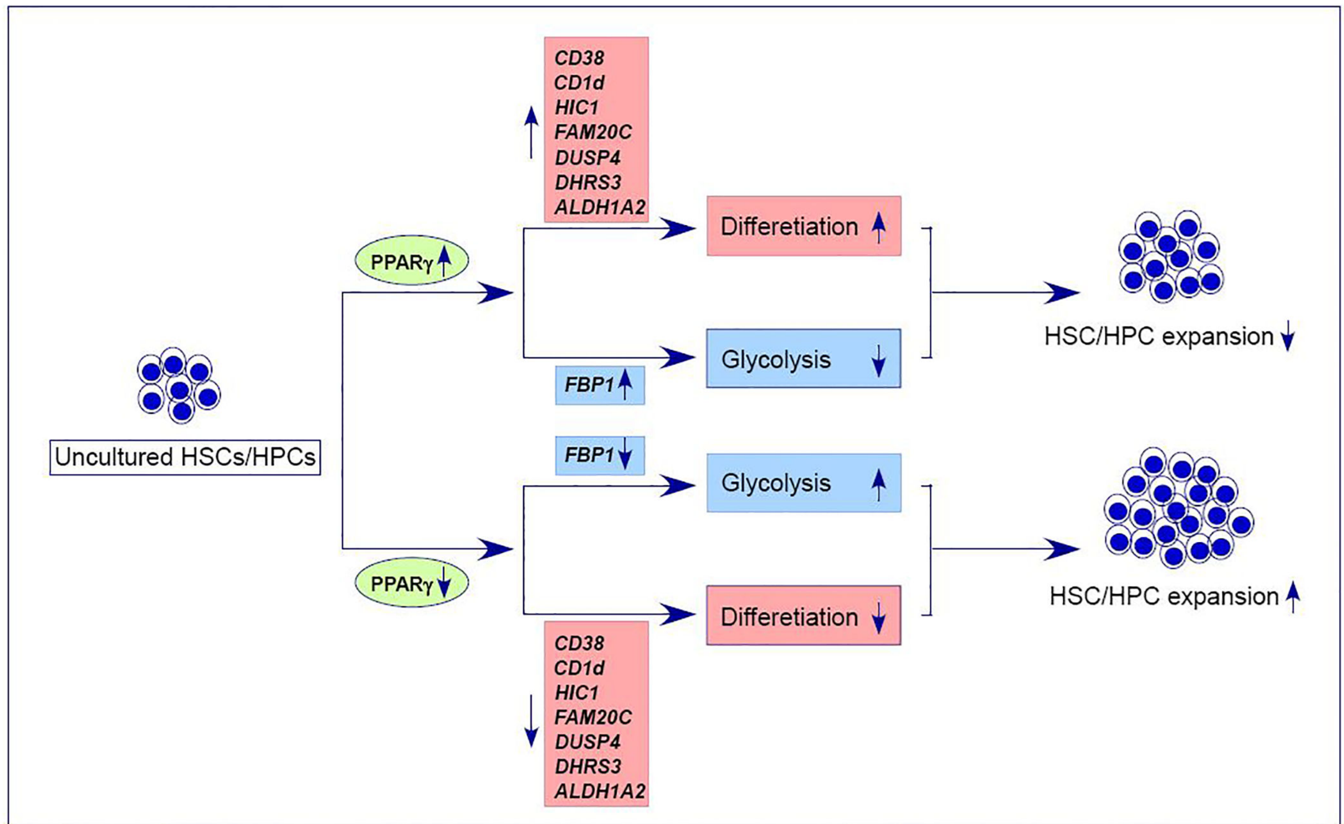

FIGURE 2.

PPARγ functions as a negative regulator of human CB HSC maintenance and expansion. During *ex vivo* culture in regular medium (RPMI1640+10% FBS+Cytokines), PPARγ signaling is activated. Activation of PPARγ increases expression of differentiation associated genes including *CD38*, *CD1d*, *HIC1*, *FAM20C*, *DUSP4*, *DHRS3* and *ALDH1A2*; and a negative regulator of glucose metabolism *FBP1*. HSCs/HPCs will not be well maintained and expanded due to increased differentiation and repressed glucose metabolism. Antagonizing PPARγ signaling enhances maintenance and expansion of human HSCs/HPCs by preventing differentiation and switching on FBP1-repressed glycolysis [60**].