Pleiotropic effects of Prostaglandin E₂ in hematopoiesis; Prostaglandin E₂ and other eicosanoids regulate hematopoietic stem and progenitor cell function

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Abstract

Eicosanoids have been implicated in the physiological regulation of hematopoiesis with pleiotropic effects on hematopoietic stem cells and various classes of lineage restricted progenitor cells. Herein we review the effects of eicosanoids on hematopoiesis, focusing on new findings implicating prostaglandin E₂ in enhancing hematopoietic stem cell engraftment by enhancing stem cell homing, survival and self-renewal. We also describe a role for cannabinoids in hematopoiesis. Lastly, we discuss the yin and yang of various eicosanoids in modulating hematopoietic stem and progenitor cell functions and summarize potential strategies to take advantage of these effects for therapeutic benefit for hematopoietic stem cell transplantation.

Keywords
eicosanoids; hematopoietic stem cells; transplantation; hematopoietic stem cell homing; stem cell engraftment

Introduction

Higher organisms maintain adequate numbers of blood cells throughout their entire lifespan to meet the normal physiological requirements of blood cell turnover, as well as respond to increased demand such as injury or infection. In man, approximately 1 trillion blood cells are produced every day, including 200 billion erythrocytes (red blood cells (RBCs)) and 70 billion neutrophils. This life long process is termed hematopoiesis. Stochastic and instructive mechanisms play important active roles in maintaining steady hematopoiesis and response to hematopoietic stress.

The hematopoietic stem cell (HSC) is at the center of blood cell production, having the capacity to produce all mature circulating blood cells, i.e., erythrocytes, platelets, lymphocytes, monocytes/macrophages, and all types of granulocytes. HSCs are defined by two fundamental characteristics: the ability to self-renew; i.e., the ability to form new HSCs, and the ability to differentiate through multilineage and lineage restricted hematopoietic...
progenitor cells (HPC) into all mature blood lineages. Breakthrough studies in the 1960’s by Till and McCulloch and colleagues showed that single clonogenic cells existed within the bone marrow that could self-renew and restore hematopoiesis [1–5] postulating the in vivo existence of a hematopoietic stem cell. These assays enumerated macroscopic nodules, colony-forming units-spleen (CFU-S) that formed on the spleens in proportion to the number of bone marrow cells injected [1]. While the hypothesis that CFU-S were HSC has turned out not to be true, rather they are more differentiated multipotent progenitor cells, these studies laid the groundwork for clinical hematopoietic transplantation. What is now clear is that the only true measure of HSC function is the ability to fully repopulate a lethally irradiated host. Assays that assess long-term repopulating cells (LTRC), an HSC synonym, utilize a donor HSC graft admixed with a competing congenic graft and markers distinct for the donor and competitor graft to distinguish blood production from each source of cells and calculation of competing repopulating units, a measure of HSC [6,7]. When compared in limiting-dilution, the frequency of competitive repopulating units (CRU) contained within the test graft can be determined by Poisson statistics [8–10]. Recently, it has become clear that HSCs are a heterogeneous population and classes of HSC with short (up to 16 weeks), intermediate (up to 32 weeks) and long-term (>32 weeks) [11] engraftment capabilities have been characterized. In light of these various potentials for self-renewal, the most stringent test of HSC potential, specifically the long-term HSC, is serial transplantation from primary recipients into secondary recipients, or beyond.

Before the advent of transplantation assays for HSC function, in vitro assays for culturing hematopoietic cells allowed many of the developmental pathways involved in hematopoietic homeostasis to be identified and the regulatory hematopoietic factors directing this process to be identified and cloned. These colony-forming cell assays identify populations of hematopoietic progenitor cells with distinct lineage-restricted differentiation patterns characterized by the type of colonies formed in semi-solid media. These colonies were determined to be clonally derived [12] and functionally distinct, establishing the beginnings of a hierarchical model. Alongside transplantation and clonogenic colony assays, development of monoclonal antibodies that define phenotypic markers of various hematopoietic cells has enabled placement of the various hematopoietic populations along a differentiation hierarchy, or “hematopoietic tree” (Figure 1).

HSCs reside in very defined and limited microenvironments, or “niches” in the bone marrow [13], and signals within these niches direct HSC maintenance. Osteoblasts are a significant regulatory component of the endosteal bone marrow niche [14–17]. Adhesion molecules, including, but not limited to, integrins, selectins, cadherins, osteopontin and CD44, as well as other receptors, contribute to HSC and HPC tethering in the bone marrow [18]. Perhaps the most important axis regulating HSC and HPC tethering and trafficking to and from the bone marrow niche, is the interaction between the CXC chemokine receptor 4 (CXCR4) and its ligand stromal cell-derived factor-1α (SDF-1α) [19,20].

Hematopoietic stem cell transplantation is routinely used to treat leukemias, cancer, hematologic diseases and metabolic disorders; however, long term blood reconstitution with some sources of HSCs is limited by inadequate number, inability to migrate/home to marrow niches, and poor engrafting efficiency and self-renewal [21–23]. An appropriate bone marrow niche is required for HSCs to self-renew and differentiate and only HSCs homing, i.e., trafficking from the peripheral blood after injection to the bone marrow niche, are able to repopulate a lethally irradiated recipient long-term [24,25]. Homing is a rapid process, which is measured in hours (or at most 1–2 days) and is distinct from the concept of “engraftment”, which is more a description of the culmination of events pre- and post-homing.
Hematopoietic stem and progenitor cells normally reside within the bone marrow, while the mature cells they produce exit the marrow and enter the peripheral blood. Evidence over the last several decades clearly demonstrates that HSC and HPC also exit the bone marrow niche and traffic to the peripheral blood [26–31]. This natural trafficking of HSC and HPC to the peripheral blood can be enhanced after chemotherapy treatment, or with pharmaceutical agents like granulocyte-colony stimulating factor (G-CSF) [28,29]. These “mobilized” cells can then be collected by apheresis and are widely used for autologous and allogeneic transplantation.

**Pleiotropic Effects of Prostaglandins on Hematopoiesis**

Numerous studies spanning the 1970s to 1990s documented physiological regulatory roles for prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) in hematopoiesis. Extensive work by us and others demonstrated that PGE inhibited the *in vitro* growth of human and mouse HPC, defined as colony forming unit-granulocyte/macrophage (CFU-GM) [32–37]. We also showed that PGE acted as a negative regulator of myeloid expansion to counterbalance positive signaling from the colony-stimulating factors in order to maintain appropriate HPC proliferation [38,39] forming a selective feedback inhibition loop [37]. This physiological role of PGE<sub>2</sub> in hematopoiesis and negative feedback regulation on myelopoiesis was documented by studies in mice differing in PGE synthetic capacity [39,40]; documentation of abnormal PGE<sub>2</sub> responses in leukemia patients [32,33,36,41,42]; prognostic association of disordered PGE<sub>2</sub> response in patients with myelodysplastic syndromes (MDS) [43]; abnormal HPC response in patients cured of germ cell tumors but progressing to acute leukemia [44]; and association of HPC response to PGE<sub>2</sub> with clinical response to Interferon-γ in chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), and Hodgkin’s disease patients [45,46]. Repetitive *in vivo* PGE<sub>2</sub> administration validated inhibition of CFU-GM frequency and cell cycle rate, with decreased marrow and spleen cellularity [47–49]. The effects of PGE<sub>2</sub> on myeloid HPC were considered to be direct [50]; however, we later showed that PGE<sub>2</sub> could induce F4/80<sup>+</sup>, Gr-1<sup>+</sup>, Mac-1<sup>+</sup>, myeloid suppressor cells, particularly when administered *in vivo* [49,51,52].

In contrast to effects on myelopoiesis, PGE<sub>2</sub> stimulates erythropoiesis by increasing erythropoietin production by the kidney [53] and by enhancing proliferation of the erythroid progenitor cells (BFU-E) [54–58]. Similarly, we showed that PGE<sub>2</sub> enhances proliferation of multipotential progenitor cells that give rise to granulocytes, erythrocytes, monocytes and megakaryocytes (CFU-GEMM) [55,57]. In additional studies, we showed that PGE<sub>2</sub> increased BFU-E and CFU-GEMM, which could be direct [59] or mediated through factors released by T cells [56,57,59].

Dendritic cell (DC) homeostasis, like all mature blood cells, is maintained via hierarchal generation from hematopoietic precursors and recent studies from our lab (P Singh and LM Pelus, unpublished) show that PGE<sub>2</sub> regulates DC-committed progenitor cells and is required for optimal *in vivo* DC development.

While it is well established that prostaglandins have inhibitory effects on mature lymphocyte functions, PGE<sub>2</sub> has thus far only been shown to inhibit B cell lymphopoiesis, having effects on pre-B cells [60,61]. Moreover, prostaglandins and cyclooxygenase enzymes present in stromal cells can regulate B lymphopoiesis [62].

**Prostaglandins and Stem Cells**

While much of the early biology of the effects of prostaglandins focused on progenitor cells, mainly owing to a lack of models to enumerate stem cell function, early studies clearly suggested that PGE<sub>2</sub> likely affected HSC function and these effects were independent from...
effects on progenitor cells. Studies by Fehrer and Gidali in 1974 showed that treatment of murine marrow cells in vitro with PGE$_2$ increased day 9 CFU-S in cell cycle that was cAMP independent [63]; however, in vivo dosing of PGE$_2$ in mice led to little or no increase in hematopoiesis [64]. An increase in CFU-GM in S-phase was also seen after PGE$_2$ pulse exposure of human marrow [65]. In 1982, we showed that short-term exposure of human or mouse bone marrow to PGE$_2$ in vitro stimulated the production of cycling CFU-GM from a population of quiescent, non-cycling cells, most likely stem cells, which were dependent on time course and concentration of PGE$_2$ [50] and were cAMP independent [66]. Kinetics of PGE$_2$ exposure were critical for stimulatory versus inhibitory effects on HPC frequency and cell cycle and as little as 3 hour exposure of bone marrow cells to PGE$_2$ increased the production of CFU-GM [66]. These findings were also recently validated with umbilical cord blood (UCB) cells, another source of HSC [67]. PGE$_2$ treatment of purified human blood CD34$^+$ cells was also shown to increase both myeloid and erythroid progenitor formation [68]. However, while highly suggestive, earlier studies did not directly measure HSC function. Recently, a requirement for PGE$_2$ for development of hematopoiesis was found in a zebrafish screen [69] and ex vivo pulse exposure to the PGE$_2$ derivative, 16,16- dimethyl PGE$_2$ (dmPGE$_2$) was shown to increase the repopulating capacity of murine bone marrow cells and increase zebrafish kidney marrow recovery, validating the hypotheses proposed in the 1980’s. However, mechanisms for increased engraftment and recovery were not determined.

PGE$_2$ increases long-term stem cell engraftment

Analysis of HSC frequency by Poisson statistics in either conventional limiting-dilution congenic transplant models in mice [69] or in a more refined limiting-dilution model in hybrid congenic mice that permits head-to-head comparison of the HSC populations [70] show a 4-fold increase in HSC frequency as a result of short-term ex vivo exposure of marrow to dmPGE$_2$ and strongly suggest a direct effect on HSC. At 5 months post-transplant, analysis of peripheral blood chimerism showed significantly higher levels of white blood cells derived from dmPGE$_2$-treated marrow cells, with full myeloid cells and B and T lymphocyte reconstitution with no obvious lineage bias [70]. Transplant of marrow from primary transplant recipients into secondary recipients and secondary recipients into tertiary recipients, all without any further ex vivo manipulation, validated the self-renewal capacity of ex vivo dmPGE$_2$-treated repopulating cells [70] and indicates that the effect of dmPGE$_2$ pulse-exposure is stable and manifested on the long-term repopulating stem cell population (LT-HSC). Transplantation of human hematopoietic cells in immunodeficient mice offers a model system to evaluate human HSC function in vivo [71]. In a similar fashion to that shown using mouse bone marrow cells, short-term ex vivo pulse exposure to dmPGE$_2$ was recently demonstrated to enhance engraftment of human umbilical cord blood HSC in NOD/SCID-IL2-γ-receptor null (NSG) mice [67]. It is important to note that these positive results on LT-HSC in the context of hematopoietic transplantation are the result of ex vivo treatment with dmPGE$_2$, and are in slight contrast to an earlier in vivo study [64] and more recent study [72] using in vivo treatment with PGE$_2$ where the enhancement by PGE$_2$ was lost in competitive transplants in the long-term. These data suggest that the combined effects of extended in vivo PGE$_2$ treatment acting directly through EP receptors on HSC and indirectly through modulation of the HSC niche in bone marrow has effects that differ from a short ex vivo pulse exposure of HSC to PGE$_2$. Further studies exploring the role of in vivo versus ex vivo treatment with PGE$_2$ and its analogues are likely to lead to refinements in clinical strategies for improving hematopoietic function and transplantation.

PGE$_2$ increases HSC CXCR4 and migration to SDF-1α and homing efficiency

Effects on homing, apoptosis or proliferation can positively or negatively alter HSC function and hematopoietic transplantation. Since we previously showed that PGE$_2$ can have dual
effects on hematopoiesis [50,66] we sought to define its mechanism of action in enhancement of hematopoietic engraftment to better understand the potential clinical utility of transient \textit{ex vivo} dmPGE exposure. We demonstrated that pulse-exposure of mouse and human stem and progenitor cells to dmPGE increases CXCR4 expression and significantly enhances migration to SDF-1α indicating that CXCR4 up-regulation on HSC coincides with enhanced migratory function. This enhancing effect of dmPGE on chemotaxis to SDF-1α was also blocked by AMD3100, a selective CXCR4 antagonist, further indicating a primary role for the CXCR4 receptor. These results are consistent with previous reports indicating that PGE\textsubscript{2} increases CXCR4 expression in microvascular endothelial cells through stimulation of transcription factor binding to Sp1-binding sites [73], and that EP3/EP4 signaling in tumor stromal cells modulates CXCR4 signaling [74]. In addition, it has been reported that a PGE\textsubscript{2} mediated increase in cAMP increases human CD34\textsuperscript{+} cell CXCR4 expression through a PKC-zeta signaling pathway [75].

As described earlier, successful hematopoietic reconstitution requires that administered HSC traffic/home to bone marrow niches where they can engraft, and the CXCR4/SDF-1α axis is a critical component of this homing process. We hypothesized that dmPGE\textsubscript{2}-induced enhancement of CXCR4 expression and migration to SDF-1α may increase \textit{in vivo} homing of HSC, providing a mechanistic insight into the enhanced hematopoietic engraftment. Pulse-exposure of enriched mouse HSC to dmPGE\textsubscript{2} \textit{ex vivo} increased their bone marrow homing efficiency by 2-fold compared to cells treated with control vehicle when directly compared head-to-head in congenic hybrid mice. Increased homing of more differentiated cells was not observed when similarly evaluated, suggesting that the enhanced homing effect of dmPGE\textsubscript{2} is specific to HSC. Similarly, dmPGE\textsubscript{2} pulse exposure of human cord blood HSC significantly enhanced their homing efficiency in NSG mice [70,76].

\textbf{PGE\textsubscript{2} decreases apoptosis}

While dmPGE\textsubscript{2} enhanced the homing ability of HSC 2-fold over control, the enhancement seen in hematopoietic engraftment was 4-fold, suggesting other mechanisms mediating HSC engraftment were involved. Apoptosis is an important regulatory process in normal and malignant hematopoiesis and PGE\textsubscript{2} signaling has been implicated in anti-apoptotic effects in many cell types [77–79]. Pulse-exposure to dmPGE\textsubscript{2} reduced Annexin-V and active caspase-3 levels in mouse and human HSC, suggesting that the enhancement of HSC function by dmPGE\textsubscript{2} could result from enhanced HSC survival [70,76]. Consistent with reduced levels of active caspase-3, intracellular levels of the endogenous caspase-3 inhibitor Survivin were significantly higher in both mouse and human HSC, consistent with our previous findings that Survivin regulates apoptosis and proliferation in HSC [80,81] and studies by others that PGE\textsubscript{2} can increase Survivin levels in cancer cells [82,83]. QRT-PCR analysis of treated HSC also showed similarly elevated levels of Survivin mRNA [70].

\textbf{PGE\textsubscript{2} increases entry of HSC into cell cycle}

We previously showed that Survivin regulates HSC cell cycle entry and progression [80,81]. Early studies by us and others also showed that PGE\textsubscript{2} can regulate the cell cycle of hematopoietic progenitors [50,63,65]. This suggests that an increase in HSC self-renewal and proliferation might contribute to the enhanced engraftment by dmPGE\textsubscript{2}-pulsed cells. \textit{In vitro} exposure of highly purified primitive mouse LT-HSC to dmPGE\textsubscript{2} significantly increases the proportion of LT-HSC in cell cycle (G\textsubscript{1} + S/G\textsubscript{2}M) compared to controls. No significant effect on the cell cycle rate of HPC or more differentiated cells was observed, strongly suggesting that the effects of dmPGE\textsubscript{2} on cell cycle rate are selective to HSC. To confirm the effect of dmPGE\textsubscript{2} on enhancement of HSC cell cycle observed \textit{in vitro}, bone marrow cells were pulsed with dmPGE\textsubscript{2} and injected into congenic mice treated with BrdU post-transplant, and the proportion of donor BrdU\textsuperscript{*} HSC determined 16 hours later. A ~2-
fold increase in the proportion of homed HSC in S+G2/M phase was observed for cells pulsed with dmPGE2 prior to transplant, confirming that short-term exposure of HSC to dmPGE2 stimulates HSC to enter and progress through cell cycle in vivo [70]. These studies suggest a model in which the coordinated effects of dmPGE2 treatment on homing, survival and proliferation lead to the 4-fold enhanced hematopoietic engraftment.

**Other Eicosanoids also affect Hematopoiesis**

While most studies have focused on the effects of prostaglandins on hematopoiesis, the effects of other eicosanoids has not gone without notice. Like prostaglandins, leukotriene B4 (LTB4) and the cysteinyl leukotrienes are produced in the marrow microenvironment [84], by hematopoietic stromal cell cultures and by freshly isolated bone marrow mononuclear cells [85]. The 5’-Lipoxygenase (5’LOX) enzyme is also detected in hematopoietic progenitor cells [86].

LTB4 is a potent stimulator of granulocyte chemotaxis [87,88], while LTD4 stimulates chemotaxis and transendothelial migration of human HSC [86]. While PGE2 inhibits myeloid progenitor cells in vitro, LTB4, LTC4 and LTD4 increase mouse and human progenitor cells [89–91]. Cyclooxygenase (COX) inhibitors also enhance myeloid progenitor cell proliferation whereas 5’-LOX inhibitors reduce myeloid progenitor cell proliferation [89,90,92]. Moreover, PGE stimulates early and late erythroid progenitor cells [57,58], while LTB4 and LTC4 inhibit them, and LOX inhibitors enhance erythroid progenitors [93]. In mice, dual COX inhibition enhances HPC recovery [92], while selective 5’-LOX inhibitors decrease CFU-GM and blast colony forming cells [89], suggesting an effect on a cell population more primitive than the CMP and CLP. The addition of LTB4 to UCB cells cultured with growth factors reduces total HSC produced and enhances HPC proliferation, whereas antagonism of the LTB4 receptor enhances production of HSC and blocks HPC proliferation [94]. Recently, deletion of 12/15-lipoxygenase was shown to reduce canonical Wnt signaling, leading to a reduction in HSC quiescence and hematopoietic defects [95].

While the cannabinoids have effects on mature cells of the immune system [96,97] it is becoming clear that they also have effects on earlier hematopoietic cells. Anandamide can act as a synergistic growth factor for hematopoietic progenitor cells [98] but promotes erythroid apoptosis [99]. 2-arachidonoylglycerol (2-AG) also stimulates progenitor cells [98] and hematopoietic cells expressing the cannabinoid CB2 receptor migrate in response to 2-AG [100]. Recently, 2-AG has also been shown to increase CFU-GEMM colony formation and cell migration [101], and activation of cannabinoid receptors on murine embryonic stem cells (ESC) promotes hematopoietic differentiation [102].

It is clear that prostaglandins, leukotrienes and cannabinoids have important roles in hematopoietic homeostasis, and evaluating their responses is critical to understanding eicosanoid function and development of eicosanoid-based therapeutic strategies for improvements in hematopoietic transplantation. While this review has focused on a few key players, there are abundantly more bioactive eicosanoids which regulate hematopoiesis with potential therapeutic benefit to cure diseases (as reviewed in [85,103,104]). While cyclooxygenase enzymes and their products are expressed in early and late erythroid progenitors and clearly regulate erythropoiesis [105], cytochrome P450 derived eicosanoids also effect erythropoiesis. Studies by Abraham et al. demonstrated that picomolar concentrations of the cytochrome P450 arachidonate metabolites, 19- and 20-hydroxyeicosatetraenoic (HETE) acid, increased CFU-E growth 4 to 6 fold, with 20-HETE being considerably more potent [106]. Recently, 20-HETE was also shown to regulate the chemotactic response of endothelial progenitor cells to SDF-1α [107], possibly suggesting a
The role of yet another eicosanoid in trafficking of hematopoietic cells. Intriguingly, even the lipid substrate for eicosanoid enzymes can alter biologic effects, as omega-3 derived fatty acids vary considerably from omega-6 derived products [108]. Recently, it was demonstrated that mice fed a diet high in omega-3 fatty acids had reduced CFU-M and CFU-GM, yet had increased common myeloid progenitors [109]. Clearly, furthering our understanding of the interactions and molecular pathways of the plethora of eicosanoids and their role in hematopoietic regulation are likely to lead to advances in clinical therapies.

**The Yin and Yang of Prostaglandins and Endocannabinoids in Hematopoiesis**

In many physiological systems, prostaglandins, leukotrienes and endocannabinoids exhibit compensatory or opposing roles [110]. Prostaglandins and leukotrienes have numerous opposing roles in pulmonary fibrosis [111], whereas in other systems they act coordinately [112]. We and others have shown that cannabinoids reduce signaling through the CXCR4 receptor [110,113,114] and as a consequence reduce neutrophil migration [115,116]. This is in contrast to PGE$_2$ that up regulates CXCR4 expression [70,76,110], suggesting that prostaglandins and endocannabinoids can act in opposing fashion in hematopoiesis. Analysis of cannabinoid receptor expression using numerous antibodies and flow cytometry showed that they are expressed on mouse and human HSC. Utilizing the dual cannabinoid receptor agonist CP55940 we found that it reduced both CXCR4 and the adhesion molecule very late antigen-4 (VLA-4) expression on mouse HSC, while dmPGE$_2$ increased expression of CXCR4 and VLA-4 expression [110]. These data support a yin and yang role for cannabinoids and prostaglandins on hematopoietic cells and the reduction of CXCR4 by cannabinoid agonism suggested that they may facilitate un-tethering of HSC and HPC from bone marrow niches that could be used to mobilize stem cells. In a further series of studies, we found that single administration of the CB$_2$ selective agonist GP1a and the dual CB$_1$/CB$_2$ agonist CP55940 but not the CB$_1$ selective agonist ACEA significantly mobilized hematopoietic progenitor cells to the peripheral blood and that the addition of a single dose of CP55940 to a standard 4-day mobilizing regimen of G-CSF significantly increased progenitor cell mobilization compared to G-CSF alone [110]. Two separate reports by Jiang et al. have also now demonstrated that cannabinoid signaling mediates mobilization, and that endocannabinoids are expressed in bone marrow and increase HPC migration and proliferation in vitro [117,118].

**Summary**

In *vivo* analysis of the effects of short-term pulse exposure to dmPGE$_2$ clearly demonstrates that it has direct and stable effects on HSC function. Enhancement of HSC frequency and engraftment by dmPGE$_2$ results from effects on HSC homing and cell cycle activity involving up-regulation of CXCR4 and Survivin, with increased chemotactic response to SDF-1α and reduced apoptosis. The ability to facilitate homing, survival and proliferation of HSC by short-term *ex vivo* dmPGE$_2$ exposure offers an exciting clinical translation strategy to improve hematopoietic transplantation, especially in transplant settings characterized by low HSC numbers, such as umbilical cord blood and some mobilized peripheral blood stem cell products. Our experimental preclinical limiting dilution transplant studies show that equivalent engraftment is achieved with four-fold fewer dmPGE$_2$-treated cells compared to untreated cells. Homing and migration studies utilizing UCB HSC also clearly support potential translation of short-term dmPGE$_2$ exposure to human hematopoietic grafts. Clinical analysis of the ability of dmPGE$_2$ to enhance engraftment of UCB is currently ongoing [119].
The available data suggest that LTB4 signaling decreases HSC self-renewal and increases differentiation, while blocking LTB4 receptors increases self-renewal and blocks differentiation. Thus, the use of a leukotriene receptor antagonist or LOX inhibitor in the post-transplant setting may favor self-renewal.

The effects of cannabinoids on hematopoietic stem and progenitor cell mobilization suggest that they can be modulated for therapeutic benefit. The fact that signaling through the CB receptors on hematopoietic cells can have effects opposite to PGE2 suggests several improvements to therapeutic strategies. Since CB signaling inhibits CXCR4 mediated migration while dmPGE2 exposure up regulates CXCR4 expression, combination use of ex vivo dmPGE2 exposure plus CB receptor antagonism may improve hematopoietic stem cell homing. Similarly, while dmPGE2 production within the bone marrow may provide signals enforcing cell retention through up regulation of CXCR4 and VLA-4, inhibition of PGE2 receptor signaling coordinate with agonizing CB receptors may facilitate acquisition of mobilized hematopoietic stem and progenitor cells for transplantation.

The availability of FDA approved pharmaceuticals that specifically regulate biosynthesis and signaling of prostaglandins, leukotrienes, cannabinoids and other eicosanoids will facilitate rapid translation of eicosanoid based therapeutic research, both at the level of improving the yield of a hematopoietic graft or measured in terms of graft performance.

### Highlights

- Short-term pulse exposure of hematopoietic stem cells (HSC) to dmPGE2 enhances their frequency and engraftment resulting from effects on HSC homing and cell cycle activity involving up-regulation of CXCR4 and Survivin, with increased chemotactic response to SDF-1α and reduced apoptosis.
- Short-term pulse exposure of hematopoietic stem cells to dmPGE2 has direct and stable effects on HSC function.
- The ability to facilitate homing, survival and proliferation of HSC by short-term ex vivo dmPGE2 exposure offers an exciting clinical translation strategy to improve hematopoietic transplantation.

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Figure 1.
Blood cell development is a hierarchical process with self-renewal and maturational divisions occurring as a continuum under the direction of single or multiple growth factors. Shown is a simplistic representation incorporating current understandings of the hematopoietic process. Specific progenitor cells include the common lymphoid progenitor (CLP), common myeloid progenitor (CMP), granulocyte-monocyte progenitor (GMP), megakaryocyte-erythrocyte progenitor (MEP), the megakaryocyte (CFU-Meg) and erythroid (BFU-E) progenitors and the common macrophage and dendritic cell progenitor (MDP).