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Enhancing engraftment of cord blood cells via insight into biology of stem/progenitor cell function

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Abstract

Cord blood (CB) transplantation has been used over the last 24 years to treat patients with malignant and non-malignant disorders. CB has its advantages and disadvantages compared to other sources of hematopoietic stem (HSCs) and progenitor (HPCs) cells for transplantation. More knowledge of the cytokines, and intracellular signaling molecules regulating HSCs and HPCs could be used to modulate these regulators for clinical benefit. This review provides brief information on the field of CB transplantation and studies from the author's laboratory that focus on regulation of HSCs and HPCs by CD26/DPPIV, SDF-1/CXCL12, the Rheb2-mTOR pathway, SIRT1, DEK, cyclin dependent kinase inhibitors, and cytokines/growth factors. It also briefly discusses cryopreservation of CB HSCs and HPCs.

Keywords

Cord blood; stem and progenitor cells; intracellular signals; cytokines

Introduction

Cord blood (CB) has served as a transplantable source of hematopoietic stem and progenitor cells to treat malignant and non-malignant disorders since our initial laboratory,[1–9] and clinical studies[10–14] over 20 years ago. There have now been over 25,000 CB transplants performed worldwide,[15] since our initial clinical report in which a child with Fanconi anemia was successfully treated with CB from his HLA-matched sister.[10] The field has moved rapidly, and advances in CB banking[16–22] and transplantation[23–44] have been encouraging, but there is still much to be learned to make CB transplantation a more efficient and efficacious procedure.[15,45]

There are advantages to using CB as a source of transplantable cells over that of other sources of hematopoietic stem (HSCs) and progenitor (HPCs) cells. This includes that CB is a readily available source of HLA-typed cells being stored in CB banks, they have already been used to treat essentially all malignant and non-malignant diseases that can be treated by bone marrow (BM) transplantation, and CB transplantation induces a lowered level of acute and chronic graft versus host disease (GVHD) when used as a single minimally manipulated unit. This latter characteristic of CB cells allows for more flexibility in related and unrelated donors using partially HLA-mismatched CB, than that used in BM transplantation. There are also disadvantages to using CB as a source of transplantable HSCs and HPCs. CB

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Conflicts of interest
The author is on the Medical Scientific Advisory Board of CordUse, a cord blood banking company.

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transplantation is associated with a slower time to neutrophil and platelet engraftment, and to immune cell recovery than that of BM and mobilized peripheral blood (mPB), events at least in part due to the more limiting numbers of HSCs and HPCs in CB collections compared to that in BM and mPB. For BM and mPB one can collect many cells, but with CB what is collected at the birth of a baby is all that is available, although, it is possible that means to collect greater numbers of CB cells at the child's birth may be feasible in the future.[46] However, at present, the lesser number of HSCs and HPCs collected in single CB units is somewhat problematic for single CB unit transplantation for adults and higher weight pediatric recipients, and CB transplantation has been associated with enhanced graft failure.

A number of investigators, including our own group, have worked on means to enhance the engraftment of limiting numbers of HSCs and HPCs, in a basic science laboratory setting, in pre-clinical animal studies, and in pilot, phase I, and other clinical studies. Examples of such attempts to foster a more potent CB transplant have been recently reviewed by experts in the field in very recent updates and include: double CB transplantation,[40–43, 47–50] *ex vivo* expansion of HSCs and HPCs,[51–54] intrabone transplantation,[55–57] and efforts to enhance the homing and engrafting of cells through *ex vivo* or *in vivo* inhibition of CD26, a Dipeptidylpeptidase (DPPIV),[58–66] incubation of cells *ex vivo* with Prostaglandin E,[67–70] or by fucosylation of donor cells *ex vivo*.[71,72]

Ultimately, a better understanding of the biology of HSCs and HPCs will allow for more innovative means to enhance the homing and engraftment of limiting numbers of HSCs and HPCs in CB. Our knowledge of the characteristics and functions of HSCs and HPCs is becoming clearer. We now know much more about the phenotypic,[73] and functional[74,75] characteristics of human HSCs and HPCs, the cytokines that regulate these cells,[76,77] and the BM microenvironmental cells and factors that influence HSCs and HPCs *in vivo*.[78–80]

This review mainly focuses in on some of the more recent work from our laboratory that evaluates intracellular and extracellular factors that influence HSC/HPC function, with the goal to eventually utilize this information to enhance the engrafting capability of HSCs and HPCs for clinical advantage. Through all of this work and for eventual translation of these studies from the lab to the clinic the goal is: "The simpler, the better." The topics of research from our laboratory to be discussed include: inhibition of CD26/DPPIV, intracellular molecule modulation of HSCs and HPCs, cytokine and growth factor effects on HSCs and HPCs, and cryopreservation of cord blood HSCs and HPCs.

CD26/DPPIV influence on SDF-1/CXCL12-CXCR4 axis and homing/engraftment of HSCs and HPCs

Stromal cell-derived factor (SDF)-1/CXCL12 is a well-known chemokine that acts as a chemotactic (directed cell movement) agent for HSCs and HPCs through its action on the receptor CXCR4. SDF-1/CXCL12 has been implicated in the homing, survival, and nurturing of HSCs and HPCs.[76,80–82] CD26/DPPIV is an enzyme that cleaves dipeptides from the N-terminus of proteins after a proline or alanine. SDF-1/CXCL12 is an example of a molecule that has a DPPIV cleavage site. CD26/DPPIV cleavage results in a truncated SDF-1/CXCL12 molecule that is no longer chemotactic.[58] Moreover, the truncated SDF-1/CXCL12 blocks the chemotactic activity of full-length SDF-1/CXCL12.[58] Since SDF-1/CXCL12 acts as an *in vivo* homing molecule for HSCs and HPCs,[80,81] and a number of cell types including HSCs and HPCs express CD26/DPPIV on their cell surface,[59] we reasoned that inhibition of CD26/DPPIV by small peptide molecules such as diprotin A (ILE-PRO-ILE) or VAL-PYR on the donor cells would enhance the homing and engrafting capability of limiting numbers of donor mouse BM cells in a congenic mouse model of

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competitive and non-competitive HSC transplantation.[59] This it did, results confirmed and extended by others.[60–62] These engraftment enhancing effects of CD26/DPPIV inhibition were extended to pretreatment of human $CD34^+$ donor CB[63,64] and mPB[65] cells transplanted into mice with a NOD/SCID genotype. *In vivo* inhibition of CD/DPPIV in recipient mice[65,66] was also effective in enhancing engraftment, effects also likely due to effects of DPPIV truncation on non-chemokine growth factors. We recently found that a number of colony stimulating factors (CSFs), such as GM-CSF, G-CSF, IL-3, and EPO contain DPPIV truncation sites, and that DPPIV inhibitors used to pretreat target cells expressing CD26 enhances the detectable activity of the CSFs. Also, *in vivo* use of DPPIV inhibitors allows accelerated recovery of HSCs and HPCs after stress (e.g. chemotherapy and irradiation) (Broxmeyer, *et al.*, unpublished observations; manuscript in revision). An FDA-approved CD26 inhibitor is currently being evaluated in a pilot clinical study at the Indiana University School of Medicine under the direction of Sherif Farag for its effects on enhancing the engrafting capability of single CB collections in adult patients with leukemia and lymphoma.[66]

Intracellular modulation of HSCs/HPCs

Understanding the intracellular signals involved in HSC and HPC function may lead to successful efforts to manipulate these signaling molecules for clinical benefit.

Effect of the Rheb2-mTOR pathway on HSC engraftment

Rheb is one member of the ras homologue enriched in the brain family of small ras-like GTPase molecules. Rheb cycles between active GTP and inactive GDP-bound forms. Both RHEB1 and RHEB2 are able to activate mammalian target of rapamycin (mTOR) signaling in mammalian cells. Since Rheb2 was found to be preferentially expressed in immature mouse HSCs compared to mature hematopoietic cells,[83] we evaluated effects of Rheb2 overexpression by means of a MIEG3 bicistronic retroviral vector, in mouse BM HSCs and HPCs on the functioning of these cells.[84] In this study, we identified Rheb2 as a pathway important in expansion of immature progenitor cells *in vitro* and *in vivo*. However, this expansion was accompanied by a loss of HSC activity. We felt that regulating the activity of the Rheb-mTOR pathway might allow for effective expansion of cells without their loss of HSC repopulating ability. Towards this goal, we treated human $CD34^+$ CB cells *ex vivo* with a combination of HSC expansion cytokines (SCF, FL, and thrombopoietin (TPO)) in the presence and absence of rapamycin prior to assessing the engrafting capability of these *ex vivo* cultured cells in sublethally-irradiated NOD/SCID IL-2R gamma chain null (NSG) mice.[85] *Ex vivo* rapamycin treatment of these cells in the presence of SCF, FL, and TPO greatly enhanced the engrafting capability of the $CD34^+$ CB cells. More mechanistic evaluation of these studies are warranted, as is further preclinical analysis for enhancing CB transplantation.

Tip110/p110nrb/SART3/p110 regulation of hematopoiesis

Tip110 is a Tat-interacting protein of 110 KDa that has been implicated in RNA metabolism and tumor-antigen presentation. Tip110 was found to regulate the transcription of HIV-1 and cellular genes.[86,87] It also functions as a general pre-mRNA splicing factor.[88] The various effects of Tip110 that impinged on transcription factors and cellular gene expression enticed us to evaluate a possible role for Tip110 in the regulation of hematopoiesis. Using Tip110-overexpressing transgenic mice, haploinsufficient ($Tip110^{+/-}$) mice, and means to up- and downregulate Tip110 expression in human cells through lentiviral gene transduction, we were able to demonstrate that Tip110 transgenic expression increased the numbers, cell cycling status, and survival of HPCs, while $Tip110^{+/-}$ mice manifested opposite effects to the Tip110 transgenic mice in terms of HPC function.[89] Also, $Tip110^{+/-}$ BM HPCs

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responded better, and Tip110 transgenic BM HPCs worse than control mice to recovery from the cytotoxic effects of 5-flurouracil.[89] Mechanistically, Tip110 regulated expression of CMYC and GATA2 expression, with Tip110 and CMYC regulating the expression of each other, thus linking Tip110 hematopoietic regulation to Tip110 reciprocal regulation of CMYC.[89] We also found that Tip110 was expressed in human embryonic stem (hES) cells, and that it was important for maintenance of expression of pluripotency factors such as NANOG, Oct4, and SOX2, and pluripotency of hES cells.[90] How these Tip110 effects in hES cells are mediated, and its role in induced pluripotent stem (iPS) cells remains to be investigated.

SIRT1 effects on hematopoiesis

SIRT1 is a member of the sirtuin family encompassing seven proteins and histone deacytelases, that has been conserved from bacteria to humans.[91] Mammalian sirtuins have been implicated in numerous cell functions, some with disease relevance.[92] SIRT1 is a human homologue close to the Sir2 yeast protein. We had shown that SIRT1 is involved in regulating apoptosis and Nanog expression in mouse ES cells when in the presence of LIF, at least in part by controlling the subcellular localization of the tumor suppressor p53 protein.[93] We followed up on that study by demonstrating the need for SIRT1 for differentiation of mouse ESCs in the absence of LIF, but presence of 2 mercaptoethanol.[94] A mouse ES cell line deficient in SIRT1 formed few mature blast cell colonies, and the replated cells from these colonies were defective in hematopoietic potential. There was decreased primitive and definitive hematopoiesis associated with LIF removal-induced differentiation of the $SIRT1^{-/-}$ mouse ES cell line, and this corresponded to a delayed capacity to turn off expression of Oct4, nanog, and Fgr5, and to decrease expression of β-H1 globin, β-major globin, and Scl genes. $SIRT1^{-/-}$ mice had fewer yolk sac primitive erythroid precursors, and manifested decreased embryogenesis. In adult mice, both $SIRT1^{-/-}$ and $SIRT1^{+/-}$ BM cells had decreased numbers and cycling status of HPCs, an effect most apparent when cells were cultured *in vitro* under lowered (5%), compared to normal (~20%) oxygen tension. Thus, these results linked oxygen tension and SIRT1 activity. Most recently, others have suggested that cell-autonomous SIRT1 intracellular signaling may be dispensable for adult HSC functional maintenance in mice.[95] How this above information on adult HSCs and HPCs may be used to modulate and influence engrafting capability remains to be determined. Of interest in this context is that deficiency of SIRT1 in mouse ES cells causes a downregulation of the PTEN-JNK-FOXO1 pathway with a concomitant block in reactive oxygen species (ROS)-induction of apoptosis.[96] Thus, at least in mouse ES cells, SIRT1 appears to play an important role in adjusting the PTEN/JNK/FOXO1 pathway for response to cellular ROS. Mitochondria and mitochondrial-generated ROS are important for hematopoiesis,[97,98] and it is possible that SIRT1 may still play a role in asymmetric divisions of HSCs and self-renewal,[99] especially in cases of heavy stress-induced hematopoiesis. In this regard, energy metabolism is likely crucial to normal, and especially stress-induced hematopoiesis.

We very recently assessed whether cellular energy homeostasis took part in the maintenance of pluripotency and self-renewal in mouse ES cells.[100] AMP-activated protein kinase (AMPK), one regulator for the control of energy metabolism, is activated during stress that induces exhaustion of ATP. We used 5-aminoimidazole-4-carboxyamide ribonucleoside (AICAR) and AMPK activator to demonstrate: activation of the p53-$p21^{cip1}$ pathway, decreased mouse ES cell proliferation, a G_1/S-phase cell cycle block, and decreased expression of the pluripotency markers NANOG and SSEA-1, without effects on Oct4 expression. This was associated with enhanced differentiation of erythroid cells from mES cells.

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DEK regulation of hematopoiesis

DEK is a relatively newly-defined molecule involved in a number of cellular activities, such as transcriptional repression and activation, processing of mRNA, and chromatin remodeling.[101,102] DEK is a unique molecule in that it can be found in the nuclear, yet it can also be secreted outside of the cell and influence other cell types.[101] It can act as a chemoattractant for specific mature blood cells ($CD8^+$ T cells and natural killer cells) after being released from macrophages. [103] We identified a role for DEK in hematopoiesis.[104] There were increased numbers of HPCs in BM and spleen of $DEK^{-/-}$ mice, and purified recombinant DEK protein suppressed *in vitro* colony formation by normal mouse BM and human CB HPC colony formation *in vitro*. This negative effect of DEK on HPC proliferation *in vitro* and *in vivo* was associated with decreased long-term competitive and secondary mouse HSC repopulating capacity, suggesting a positive role for DEK in HSC functions such as engraftment. What these hematopoietic effects of DEK are due to requires further investigation, but this information may be of potential clinical relevance.

Role for cyclin-dependent kinase inhibitors in hematopoiesis

A number of cyclin-dependent kinase inhibitors (CDKIs) have been implicated in HSC and HPC function.[76,105–108] These include $p21^{cip1/waf1}$ (p21), $p27^{kip1}$ (p27), and $p18^{INK4c}$ (p18). However, other than a paper demonstrating that $p18^{-/-}$ counters the exhaustion of $p21^{-/-}$ HSCs after serial transplantation,[109] there is nothing else in the literature that links the different CDKIs and their networking interactions for HSC and HPC function. We noted that CDKIs had different effects on HPC proliferation, and that they differentially modulated the responsiveness of HPCs to synergistic combinations of cytokines such as a CSF plus SCF.[110] Deletion of p18 resulted in decreased numbers and proliferation of HPCs, effects similar to that previously reported by us for $p21^{-/-}$ mice.[77] These positive effects of p18 dominated over the negative effects of p27 where $p27^{-/-}$ was associated with enhanced HPC proliferation. The responsiveness of HPCs to suppression by certain chemokine family members was directly related to the ability of HPCs to respond to synergistic stimulation, and cycling HPCs. Deletion of the p18 gene rescued the loss of chemokine suppression of synergistic cell proliferation associated with deletion of the p21 gene. Thus, there is interplay of cell cycle regulators on HPC proliferation, and loss of one CDKI can sometimes be compensated for by another missing CDKI.

Cytokine/growth factor regulation of hematopoiesis

Numerous cytokines are known to regulate the proliferation and survival of HPCs.[76,77,108]

Role of immune cells in the regulation of hematopoiesis

T lymphocytes play a role in the proliferation of HPCs and their homeostasis,[111–113] in part through the transcription factors STAT4, STAT6, BCL-6, and BAZF, and the growth factor oncostatin M. We recently reported a role for STAT3-dependent IL-21 production from helper T cells in maintenance of HPC homeostasis.[114] There was decreased activity of HPC proliferation in mice with a specific deficiency of STAT3 in T cells, and STAT3 expression was required for production of IL-21. Neutralization of IL-21, but not IL-22, resulted in a decrease in HPC number and cycling, similar to that seen in STAT3-deficient T cell mice. Moreover, exogenous administration of IL-21 was able to rescue suppressed HPC proliferation in mice with $STAT3^{-/-}$ T cells.

Angiopoietin-like molecules -2 and -3 enhance survival of HPCs in CB

Angiopoietin-lilke (ANGPLT) molecules have been implicated in regulation of mouse fetal liver and BM HSCs and human CB NOD/SCID repopulating cells,[115–117] but no information was available on effects of ANGPTL molecules on HPCs. We identified the

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actions of ANGPTL-2 and -3 molecules on enhancement of the survival and replating ability of HPCs from human CB.[118] These activities of ANGPTL-2 and -3 were manifested through the coiled-coil domains of these proteins. We did not detect functional activities of ANGPTL-4, -5, -6, or -7 on HPC survival or replating capacity, and none of the ANGPTL molecules tested influenced the proliferation of CB HPCs. The survival and replating effects of ANGPTL-2 and -3 on HPCs[118] and that of such ANGPTL molecules on expanding NOD/SCID repopulating human HPCs[116] may be of future relevance to CB transplantation.

A role for neuronally-active molecules on hematopoiesis

The nervous system has been implicated in microenvironmental control of hematopoiesis.[79] This opened up the possibility that other neuronally-associated proteins and their receptors could play a role in hematopoiesis. We identified such a role for neurexophilin1.[119] Neurexophilins bind neurexin1α. neurexin1α, and dystroglycan are membrane receptors. They serve as mutual ligands within the neuronal system. We found that neurexophilin1 was able to suppress the proliferation of HPCs, and it acted through neurexin1α, an effect that could be counter-modulated by dystroglycan. The suppressive effect of neurexophilin1 on HPCs was direct-acting on the HPCs and inhibition was apparent both *in vitro* on human CB and mouse BM HPCs, and *in vivo* after injection of recombinant neurexophilin1 into mice. Thus, a signaling axis in the hematopoietic system centered on neurexin1α and its modulation by neurexophilin1 and dystroglycan. Additional information on links between the nervous and hematopoietic systems may offer the opportunity to modulate one for the benefit of the other in a transplant setting.

Potential for modulation of intracellular signals by cytokines and growth factors and other means for enhanced CB transplantation

There are many transcription factors and other intracellular signaling molecules that impinge on HSC and HPC numbers and functions.[76,108] How all these different intracellular factors may interact with each other if at all, will need to be better elucidated if they are to be modulated for clinical advantage with minimal side-effects. Interconnected with these intracellular molecules are numerous cytokines and growth factors that can trigger/activate these intracellular molecules.[76,77] While much is known regarding cytokines and growth factor effects on HPC function, we still know very little of how these cytokines/growth factors influence HSC functions such as self-renewal, survival, and engraftment. Future information in these areas will likely have a positive influence on how we might be able to enhance HSC transplantation, especially with CB cells.

Cryopreservation of CB HSCs, HPCs, and other cells

CB transplantation is critically-dependent on CB banking, which in turn is dependent on the capacity to adequately cryopreserve the HSCs and HPCs in CB, and maintain these cells in a frozen state. Many banks, both public and private, have been formed in order to supply cryopreserved CBs for transplantation purposes. However, how long such frozen CB units can be stored and then thawed for efficient recovery of HSCs and HPCs is critical information for the success of CB banking and CB transplantation. Over the last 23 plus years we have reported on the cryopreservation and subsequent recovery of thawed cells.[1,7,120,121] Most recently, we demonstrated that we could recover functionally-intact HPCs at high efficiency from cryopreserved CB after thawing of cells stored frozen for up to 21–23.5 years.[122] While there was a range of recoveries of HPCs from different CB units, 80–100% recovery was apparent for most samples, with maintenance of high proliferative and replating capability. Moreover, CB cryopreserved for up to 21 years could be thawed,

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the $CD34^+$ cells isolated, and these cells could be used to long-term repopulate primary and secondary immune-deficient mice suggesting that long-term marrow repopulating and self-renewing HSCs had been adequately cryopreserved and could be retrieved after thawing with excellent intact functional capabilities. From the long-term cryopreserved cells, we were also able to retrieve functionally responsive $CD4^+$ and $CD8^+$ T cells, and high proliferative potential endothelial colony forming cells (=endothelial progenitor cells), and we were able to generate from the thawed and subsequently purified $CD34^+$ cell population, iPS cells that could be differentiated into all three germ cell lineages *in vitro* and *in vivo*. [122] Subsequent studies with these iPS cells found that only a percentage of these cells were fully reprogrammed. Efforts are underway to enhance the full reprogramming capacity of a larger percent of these iPS cells by modulating expression of the micro RNA 302 cluster and its downstream targets. However, how effective these generated iPS cells may be for future regenerative medicine possibilities remains to be determined.

Concluding remarks

The intent of this article was to focus mainly on laboratory and translational research in the author's laboratory. There are many outstanding laboratories working on means to gain a better mechanistic insight into optimizing the functional activities of HSCs and HPCs. It is hoped that together this work will translate into clinical utility for health benefit, with one such benefit being enhanced efficacy of cord blood HSC/HPC transplantation.

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