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Review Article

Hematopoietic stem and progenitor cells directly participate in host immune response

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Abstract: The properties of hematopoietic stem and progenitor cells (HSPCs), including self-renewal and pluripotency, have been extensively studied. These features have been explored in the management of several haematological disorders and malignancies. Although their role as precursors of innate immune cells is well understood, little is known about their direct participation in host immune response. In this review, we explicate the direct role of HSPCs in the host immune response and highlight therapeutic options for the infectious disease burden that is currently ravaging the world, including COVID-19.

Keywords: Hematopoietic, stem cells, progenitor cells, immune, haematopoiesis

Introduction

Hematopoietic stem cells (HSCs) are multipotent cells that emerge during embryogenesis [1] and give rise to lineage-restricted haematopoietic progenitor cells (HPCs). These are further differentiated into various subtypes of blood cells, including granulocytes, monocytes, and lymphocytes [2-4] which participate in host immune response. HSPCs are primarily resident in specialized niches in the bone marrow, where haematopoiesis occurs predominantly [1, 2, 5, 6]. Within these niches, HSPCs are protected by a perivascular microenvironment comprising of mesenchymal stromal cells, osteoblasts, and endothelium [2, 7]. These niches produce stromal-derived factor-1 (SDF-1), which binds to its receptor (CXCR4) on HSC surface to maintain quiescence, self-renewal, and survival [2, 5]. However, this balance is often disrupted by stressors such as infection and inflammation, which result in activation and recruitment of quiescent HSPCs to actively contribute in replenishing the peripheral needs [2, 6, 8]. In the process of combating invading pathogens, immune cells are consumed by mobilization to the site of infection [9]. Consequently, there would be an increase in peripheral demand for immune cells, which triggers HSPCs to proliferate and differentiate into myeloid and lymphoid cells to meet such demand [5]. These features of HSPCs are considered a precursor role in host immune defence. However, evidence based studies have shown that HSPCs directly partake in host immune response [5]. This attribute of HSPCs is understudied despite the promising future it holds in the management of infectious diseases, particularly the ongoing global pandemic of COVID-19. In this study, we review the immunogenic role of HSPCs and highlight its ability to act as effectors in host immune response.

HSPCs act as primary responders in host immune response

HSPCs mobilise and home to the site of infection: In homeostasis, HSPCs travel at low num-

bers through peripheral lymphatic and blood circulation. However, upon infection, inflammation, stress and injury, peripheral mobilization occurs [5]. These conditions trigger the disruption of the CXCR4/SDF-1 axis within the bone marrow niche, resulting in the liberation of HSPCs to peripheral tissue [5, 10-12]. The upregulation of G-CSF in the bone marrow endothelium by bacterial infection inhibits osteoblastic production of SDF-1 with consequent release of HSPCs [5, 13-15]. SDF-1 in peripheral tissue is also upregulated in response to infection and inflammation, constituting a gradient that may contribute to the maintenance of HSPCs within infected peripheral tissue [5, 15]. This was demonstrated in an *in vitro* study, which showed the egress of HSPCs from bone marrow directly into the blood with subsequent localization in the peripheral tissue [5, 6] where they may undergo haematopoiesis and elaborate pro-inflammatory cytokines [5]. CD34+ hematopoietic progenitor cells also express surface dopamine and β2-adrenergic receptors [5, 15, 16], which can be upregulated by myeloid cytokines such as G-CSF and GM-CSF, thereby augmenting their mobilization [5, 16].

The mobilisation of HSPCs to peripheral blood is also orchestrated by nod-like receptor family pyrin domain containing (NLRP) inflammasome [17, 18], one of the protein complexes that participates in innate immunity [19]. Several inflammasomes have been described, including NLRC4, NLRP3, AIM2 and NLRP1 [19]. NLRP3 is expressed on human HSPCs [18] and consists of a sensor molecule, the apoptosis-associated speck like protein (ASC) and procaspase-1 [19, 20]. The inactive form of this protein complex is located in the cytoplasm [18]. The NLRP3 is activated by series of endogenous agonists, including adenosine triphosphate (ATP) [20]. Upon activation, procaspase-1 protein becomes cleaved to functional caspase 1 which converts inactive pro-IL-1β and pro-IL-18 into their active forms [18] leading to secretion of mature IL-1β and IL-18. This process coupled with expression of NLRP3 inflammasome complex and activated complement cascade products propagates a sterile inflammation state in the bone marrow microenvironment which plays a crucial role in HSPCs mobilization to peripheral blood [18]. Similarly, Lenkiewicz et al. demonstrated that NLRP3 inflammasome activation can be achieved by a microbial toxin from *streptomyces hydoscopicus* (negricin) [21]. In their experiment, a prolonged administration of nigericin in mice triggered HSPC mobilization [21]. This suggests that NLRP3 inflammasome expressed in HSPCs can act as a sensor for pathogenic molecules [18]. Notably, Kucia et al. demonstrated that NLRP3 inflammasome on HSPCs responds to activation by SARS-COV-2 spike protein [22]. In contrast to mobilization, this may result in pyroptosis (inflammatory form of programmed cell death) [22], causing reduction in the HSPC pool. Inhibition of this process by NLRP3 inflammasome inhibitor could find potential clinical application in the management of COVID-19 [22].

HSPCs proliferate and differentiate as primary responders: The role of HSPCs as precursors of immune cells such as proliferation and differentiation to replenish peripheral needs is well documented. Additionally, HSPCs act as first responders without preceding peripheral demand (cytopenia) [9]. Shahbazian et al. demonstrated that infection of mice with an intrapulmonary injection of E. coli resulted in phenotypic expansion of the HSPC pool [9, 23, 24]. Similarly, the proliferation of HSPCs was observed in chronic *Mycobacterium avium* infection in association with IFN-γ [5, 25]. These *in-vitro* experiments imply that HSPCs proliferate and differentiate as part of primary immune response rather than the mere replacement of depleted peripheral pools [9, 25]. This ability to respond directly to infection is attributable to several classes of intracellular and surface signalling receptors expressed by HSPCs which bind to pathogenic ligands [26]. One of which is pattern recognition receptors (PRRs). These are proteins that are capable of recognizing pathogen associated molecular patterns (PAMPs) [2, 5, 27-31]. There are four major sub-families of PRRs that have been characterized. These are toll-like receptors (TLRs), the nucleotide-binding oligomerization domain (NOD) like receptors (NLRs), the retinoic acid-inducible gene 1 (RIG-1) -like receptors, and the C-type lectin receptors (CLRs) [31]. The two expressed by HSPCs are NLRs and TLRs, and they contribute to immune response [2, 5, 32-34].

Toll-like receptor family: These are a family of ten receptors, comprising TLR1 – TLR10 [28]. TLRs ‘1, 2, 4, 5 and 10 are localised to the cell

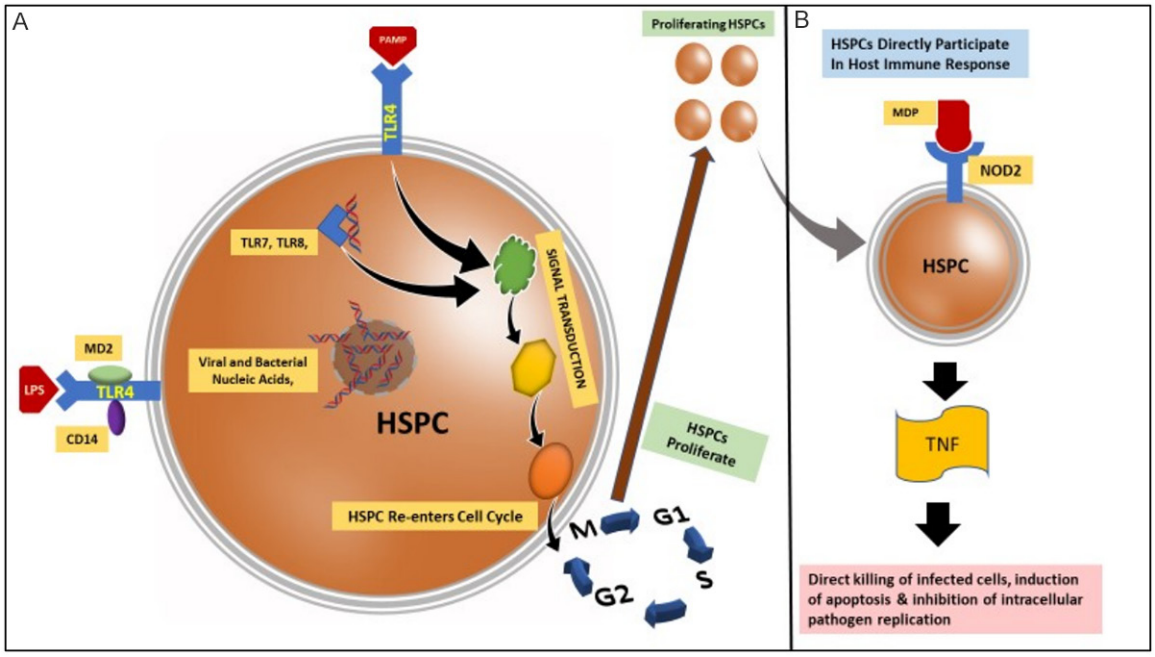

Figure 1. A. Activation of the TLR4 by the binding of the extracellular ligand PAMP (pathogen associated molecular pattern) and the intracytosolic activation of TLR7, TLR8 by bacteria and viral nucleic acid molecules result in the proliferation of the HSPCs. B. Activation of the NOD2 receptor on the HSPC by the MDP leads to the direct killing of the pathogen by the secretion of TNF.

surface whilst TLRs '3, 7-9' are found in the intracellular compartment [28, 35, 36]. Whereas cell surface TLRs recognize microbial membrane components, the intracellular TLRs recognize nucleic acids derived from bacterial and viral pathogens (**Figure 1A**) [28, 37]. Sioud et al. demonstrated that TLRs, including TLR4, TLR7, and TLR8, were expressed on freshly isolated bone marrow CD34+ HSPCs [38]. *In vivo* and *in-vitro* studies have also shown that TLR ligation induces cell cycle entry in quiescent HSPCs with resultant proliferation and differentiation (**Figure 1A**) [2, 29, 34, 38, 39]. Megías et al. demonstrated that TLR agonists can stimulate HSPCs [29, 40]. In this model, purified Lin^- or LKS+ from mice bone marrow were transplanted into mice whose native cells lack response to TLR ligands. The recipient mice were subsequently injected with ligands for TLR2, TLR4, or TLR9. The donor HSPCs were detected in bone marrow and spleen of infected mice, and these cells proliferated and differentiated in response to the TLR ligation [29, 40]. Similarly, TLRs and co-receptors such as TLR4, MD-2 and CD14, expressed by HSPCs, also detect LPS from gram-negative bacteria and the resultant TLR signalling drives differentiation of HSPCs into myeloid lineages [2, 6, 9].

Proliferation and expansion of HSPCs is also observed when PAMPs activates NLRP3 inflammasome [17, 18, 41].

HSPCs produce cytokines and chemokines: Various regulatory proteins, including T helper 2 cytokines, Kit Ligand (KL), fms like tyrosine kinase (FLT3) ligand, TGF-β1 and TGF-β2, are secreted by CD34+ hematopoietic progenitor cells [5, 42, 43]. Some of these cytokines regulate haematopoiesis in an autocrine/paracrine fashion [42]. Secreted proteins such as FLT3 ligand, KL and thrombopoietin (TPO) are known to stimulate haematopoiesis [42]. HSPCs secrete HIV-related β-chemokines that could protect against infection by R5 (macrophagotropic) HIV [42, 44, 45]. In addition, CD34+ HSPCs secrete IL-16, a protein that may interfere with HIV infection [42, 46]. They also partake in tissue remodelling and repair, through the generation of reparative growth factors, including TGF-β, epithelial growth factor, angiogenin and fibroblast growth factors [5, 43]. Interestingly, HSPCs receptors such as NLR and TLR signalling have been implicated in the production of these regulatory proteins [38, 47]. The nuclear localization receptor (NLR) consists of a family of 22 proteins in humans,

the earliest recognized of which are the NOD1 and NOD2 [47]. These are primarily expressed on immune cells, including lymphocytes, dendritic cells, and macrophages [47]. Most importantly, NOD2 expression has been recognized in CD34+ progenitor cells [5, 33, 47]. Stimulation of NOD2 on HSPCs by bacterial muramyl dipeptide (MDP) triggers the secretion of transcription factor PU.1, CD14, CD11c and GM-CSF [33]. NOD2 ligation by MDP also results in the production of TNF (**Figure 1B**) [33], a potent pro-inflammatory cytokine that induces various cellular responses through a variety of mechanisms including the direct killing of infected cells, induction of apoptosis and inhibition of intracellular pathogen replication [48]. In addition, CD34+ HSPCs stimulation by MDP led to intracellular up-regulation of α-defensin 1-3 [33, 42], which suggest that they might directly eliminate pathogenic bacteria [42]. Similarly, ligation of TLR7 and TLR8 on CD34+ progenitor cells induce IL6, IL4-β, IL8, TNF-α and GM-CSF production [38]. Interestingly, NOD2 expressed on CD34+ progenitor cells can synergize with TLRs to induce cytokine response to MDP and LPS [33]. In completion, the cytokines produced in response to ligation of HSPC receptors drives differentiation and self-renewal (haematopoiesis) as well as partake in microbial clearance and initiation of the adaptive immune response [28, 35, 37]. Although haematopoiesis can be considered an indirect or secondary function of HSPCs, microbial clearance by IFN and other cytokines is a direct effector role of HSPCs. This implies that HSPCs are direct players in host innate immunity and are contributors to the initiation of the adaptive immune response [5, 26].

Other immunogenic receptors expressed by HSPCs

Peripheral HSPCs express CD47 and PD-L1: HSPCs transiently reside in the peripheral tissue, where they directly respond to infection [5, 6, 49]. Interestingly, CD47 (an integrin associated protein) is upregulated on peripheral HSPCs [26, 50]. This protein is known to prevent phagocytosis of macrophages by binding to signal regulatory protein alpha [26, 50, 51]. Weissman group demonstrated that CD47 is detected at low levels in bone marrow resident HSPCs, but upregulation dramatically occurs after activation and peripheral mobilization [26, 50, 52]. The upregulation of CD47 on the surface of circulating HSPCs protects them from phagocytosis [52], which further attest to the immunogenicity of HSPCs [50]. HSPCs also express program death ligand-1 (PDL-1) [26], a member of the B7 family that binds with program death 1 (PD1) on T cells, thereby blocking the T cell activation. PD-L1 is typically expressed on dendritic cells, activated immune cells and on cells in immune-privileged areas such as placenta [26, 53, 54]. PD-L1 is also selectively expressed by various cellular components in the tumour microenvironment [26, 54]. Zheng et al. illustrated that PD-L1 expression is upregulated in *in-vitro* cultured HSPCs, which effectively inhibit host T cell proliferation [26, 54, 55]. The experiment of Fiorina et al. on mouse splenic Lin-Kit+ hematopoietic cells after treatment with CXCR4 demonstrate that PD-L1 on hematopoietic progenitors can be upregulated upon mobilization to peripheral site [26, 56]. Ben et al. discovered that HSPCs display defective expression of PD-L1 in type 1 diabetic patients [57]. Indeed, fewer PD-L1+ HSPCs were detectable in type 1 diabetic patient as compared to healthy controls. Pharmacological restoration of PD-L1 on HSPCs inhibited type 1 diabetes autoimmune response. Genetically modified HSPCs overexpressing PD-L1 also reverted hyperglycaemia after transplantation in a mouse model [57]. These studies, therefore, prove that HSPCs have immune privilege through their surface receptors [26] which can be targeted in immunotherapy [57].

HSPCs differentially express SLAM family receptors: The signalling lymphocytic activation molecule (SLAM) family is a subfamily of CD2 immunoglobulin comprising nine-cell surface receptors that participate in immune function [58-60]. SLAM family (SLAMF) receptors mediate intracellular protein tyrosine phosphorylation signals [61] and are widely expressed by most hematopoietic cells [60, 62]. They participate in the regulation of T lymphocyte and natural killer (NK) cells [63] and serve as costimulatory molecules on CD4+, CD8+ and NK cells [62]. They also modulate lytic activity, cytokine production, B-cell activation, and memory generation [62]. Macrophages and dendritic cells also express SLAMF receptors. Interestingly, some SLAMF receptors including CD150, CD48 and CD288 are differentially expressed by HSPCs [64]. These subsets of SLAMF receptors have been implicated in various immune func-

tions. It has been shown that CD48 contributes to the immunological process by interacting with CD2 and by forming a receptor-ligand pair with CD244 [59, 65]. CD48 is also known to activate NK cell cytotoxicity by binding to its membrane protein 2B4 [66] and regulates cytotoxic T-lymphocytes via its interaction with CD244 [59]. These processes are central to viral clearance and T cell regulation [59]. On antigen-presenting cells, CD48 interaction with CD2 contributes to adhesion and co-stimulation [59, 67-69]. Furthermore, CD48 detects microbes by binding to bacterial lectin FimH, leading to opsonin-free phagocytosis [59, 70-72]. On the other hand, CD150 serves as a receptor for the measles virus [73] and its vaccine strains [74]. The expression of CD150, CD46 and CD244 by HSPCs suggests that they may participate in immunity by demonstrating the functions of these receptors described in other immune cells.

Engineered HSPCs in immunotherapy

Engineered HSPC has been extensively explored as a therapeutic option for viral diseases [75]. Holt and colleagues achieved the disruption of CCR5 (the major HIV-1 co-receptor) by using engineered zinc finger nucleases (ZFN) on umbilical cord CD34+ HSPCs [76]. The ZFN modified HSPCs were secondarily transplanted into mice with subsequent HIV-1 challenge, and the outcome was a rapid selection for CCR5 negative cells and low levels of HIV-1 replication [76]. In a recent *in-vitro* study, Joglekar et al. engineered HSPCs to express HIV-specific T cell receptors (TCR), which inhibited HIV infection [77]. In phase II clinical trial, 74 HIV infected adults received a tat/vpr specific anti-HIV ribozyme delivered by autologous CD34+ HSPCs with resultant reduction in viral load and improvement in CD4+ count [78]. HSPC engineering has also been explored in other viral infections like lymphocytic choriomeningitis. Starck and colleagues' in an *in-vitro* study demonstrated that TCR-engineered HSPCs controlled progression of lymphocytic choriomeningitis [79]. These plausible studies, amidst many other experiments and clinical trials, support that HSPC engineering holds a future for viral immunotherapy.

Interestingly, all cells of the body, including lymphocyte progenitors, contain the TCR gene in the germ-line configuration. In contrast to mature T cells, the TCR gene cannot be expressed as TCR proteins [80]. This difference stems from the T cell developmental process in the thymus, where the products of RAG1 and RAG2 rearrange the TCR gene to a translatable and functional gene receptor [80]. Therefore, modifying the TCR gene on HSPCs to a translatable functional gene receptor may provide an option for viral immunotherapy. A similar protocol has generated antigen-specific CD8+ T cell for cancer immunotherapy [81].

HSPC Immunogenicity in current and prospective therapeutics

Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) is an established cellular therapy in haematological malignancy, including acute myeloid leukaemia (AML) [82, 83]. Evaluation of potential donors for allo-HSCT involves rigorous assessment of the human major histocompatibility complex for the identification of suitable donors [83]. MHC class I K plays a critical role in HSPCs engraftment via interaction with recipient natural killer (NK) cells [84]. Thus, the successful engraftment of donor HSPCs require MHC class I K matching between HSPC donor and recipient [84], which further supports the immunogenicity of HSPCs. Furthermore, about 24% to 34% of patients relapse after allo-HSCT [85, 86], which is primarily due to sustained commitment of recipient HSPCs to AML cell lines. In most cases, recipients HSPCs are removed by toxic conditioning agents to allow successful donor engraftment. However, Abadir et al. developed a highly potent, less toxic anti-CD300f antibody drug conjugate that selectively depletes HSPCs and AML cell lines in vitro, which may reduce relapse in allo-HSCT [85]. The CD300f is an inhibitory receptor found on HSPCs and some AML cells [85], which makes CD300f an excellent target in both AML therapy and targeted allo-HSCT conditioning [85].

Harnessing the lymphopoietic role of HSPCs in the management of COVID-19

Enhancing HSPCs' role in host immune response may provide a laudable therapy in COVID-19 management. It has been suggested that coronavirus causes immunosuppression by directly infecting HSPCs with consequent depletion of bone marrow store [87]. Recent study documented that lymphopenia is a significant clinical parameter in COVID-19, and it correlates with intensive care unit admission

Table 1. Summary of some studies showing the activity profile of HSPCs

Study	Year	Findings	Reference number
Kucia et al.	2020	NLRP3 inflammasome in HSPCs responds to SARS-COV-2 spike protein	[22]
Lenkiewicz et al.	2019	HSPCs proliferate and mobilize to peripheral blood on activation of NLRP3 inflammasome	[21]
Joglekar et al.	2018	Engineered HSPCs express HIV-specific T cell receptors which inhibited HIV infection	[76]
Ben et al	2017	Pharmacological restoration of HSPC PD-L1 reverses autoimmune diabetes	[57]
Starck et al.	2014	TCR-engineered HSPCs controlled lymphocytic choriomeningitis	[78]
Yanez et al.	2013	TLR ligation induces HSPCs cell cycle re-entry	[29]
Zheng et al.	2011	PD-L1 expression is upregulated in in-vitro cultured HSCs	[55]
Fiorina et al.	2011	Mouse splenic Lin-Kit+ hematopoietic cells upregulate PD-L1 upon mobilization	[56]
Holt et al.	2010	ZFN modified CD34+ HSPCs secondarily transplanted into mice, subsequently challenged with HIV-1 resulted in low levels of HIV-1 replication	[75]
Jaiswal et al.	2009	CD47 is upregulated on mobilized HSPCs	[52]
Sioud & Floisand	2009	Stimulation of NOD2 by MDP triggers secretion of CD14, CD11c, transcription factor PU.1, GM-CSF and TNF	[33]
Massberg et al.	2007	Egress of HSPCs directly into blood with subsequent localization in peripheral tissue	[6]
Massberg et al.	2007	Ligation of TLRs and co-receptors expressed on HSPCs drives HSPCs differentiation to myeloid lineages	[6]
Sioud et al.	2006	TLR4, TLR7 & TL8 were expressed on freshly isolated bone marrow CD34+ progenitor cells	[38]
Shahbazian et al.	2004	Infection of mice with intrapulmonary E-coli results in expansion of HSPCs	[23]

and high mortality [88]. This is particularly due to suppressed T cell immunity with a significant decrease in CD8+ T cells [88, 89]. The host ability to mount effective T cell response is therefore central to survival in COVID-19 [90]. Aging is a strong determinant factor in this process [90] which favours myelopoiesis over lymphopoiesis with increase in number of myeloid-biased HSPCs [18] and resultant shrinkage in the pool of B and T lymphocytes in hematopoietic organs [18, 91]. Increasing age also results in shrinkage of the thymus (where T cells matures) with replacement by fat, and consequently, a reduction in the number of naïve T cells exiting the thymus [92]. This reduces the host ability to mount an effective T cell response. Enhancing T cell lineage commitment of HSPCs by IL-7 immunotherapy in the early phase of SARS-COV-2 infection may be a potential treatment for COVID-19. Notably, IL-7 is a lymphopoietic cytokine, required at every stage of T cell development, differentiation, and homeostasis, and when administered, it increases peripheral naïve and central T cell pool [93]. In Fact, IL-7 was considered a prime candidate in overcoming immune inhibitory networks in chronic active infections [94]. Interestingly, IL-7 has been safely administered at 10 μg/kg in the management of a severe COVID-19 case with improvement in lymphocyte count [95]. Day 4 post administration of IL-7, PCR test for SARS-COV-2 was negative with subsequent clinical improvement [95]. This as well as other related studies show that IL-7 is a veritable therapeutic target in the management of COVID-19.

Conclusion

HSCs and the lineage restricted HPCs have been extensively studied. They are traditionally reputed as leukocyte precursors; however, evidence has shown that beyond their leukocyte ancestral role, they directly participate in host immune response (**Table 1**). HSPCs proliferate to expand self-renewal pool and they mobilize to peripheral site of infection where they may elaborate pro-inflammatory cytokines and undergo haematopoiesis. They simultaneously participate directly in host defence through their surface and intracellular receptors-TLR, NOD2, CD47 and PDL-1. Further studies will be necessary to investigate the therapeutic potentials of engineering these receptors. This will create a platform for modified HSPC transplantation in the management of overwhelming infections. The complexity of HSPC transplantation is well understood. Nevertheless, autologous HSPC transplantation in the form of, salvaged cord blood or engineered HSPCs is not associated with the challenges of HLA matching. Thus, HSPC engineering and salvaged cord blood HSPCs holds enormous potential for therapeutic use.

Disclosure of conflict of interest

None.

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