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STEM CELLS: POTENTIAL THERAPY FOR NEONATAL INJURY?

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Synopsis

Stem cell transplantation (SCT) is an established first-line or adjunctive therapy for a variety of neonatal and adult diseases. New evidence in preclinical models as well as a small number of human studies show the potential utility of SCT in neuroprotection and in the modulation of inflammatory injury in at risk-neonates. In this review we briefly summarize current understanding of human stem cell biology during ontogeny and present recent evidence supporting SCT as a viable approach for post-insult neonatal injury.

Keywords

stem cells; hematopoiesis; cord blood; transplantation; neonate; injury

Introduction

Stem cell transplantation (SCT) is an established first-line or adjunctive therapy for a variety of neonatal diseases, including those involving inborn errors of metabolism, types of primary immune deficiencies, certain neutrophil disorders, and hematologic malignancies such as neonatal leukemia. The utility of SCT in these and related conditions have been extensively discussed in the literature, and are beyond the scope of the present review[1–6]. We here briefly summarize current understanding of human stem cell biology during ontogeny and present recent evidence of the potential role of SCT for the treatment of post-insult neonatal injury.

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Stem Cell Biology: A Brief Review

Stem cell theory: Pluripotent stem cells and tissue specific somatic stem cells

Two main types of stem cells have been described: Pluripotent stem cells (PSCs) and somatic stem cells. The PSCs are multipotent stem cells that can differentiate into all cell types in the body and include *embryonic stem cells (ESCs)* and *inducible pluripotent stem cells (iPSCs)*. Tissue specific somatic stem cells give rise to organ-specific cell types. Embryonic stem cells (ESCs) are first established from the inner cell mass of the blastocysts in a fertilized egg[7–9]. *In vitro* studies have shown that cultured ESCs display self-renewal ability and have the capacity for multi-lineage differentiation. ESCs can differentiate into cell types that include all three germ layers, and *in vivo* studies have shown that ESCs can form teratomas when inoculated into immune deficient mice. Murine studies have shown that when a fertilized egg is injected with ESCs and implanted into a pseudo-pregnant dam, ESC-derived cells contribute to all embryonic cell types, forming a chimeric animal. The multi-lineage differentiation ability of ESCs both *in vivo* and *in vitro* highlights their potential utility for stem cell therapies (SCT). However, this therapeutic potential is accompanied by ethical problems since ESCs can be derived only from fertilized eggs.

More recently, embryonic stem (ES)-like pluripotent stem cells have been established from postnatal mouse testis and adult mouse/human somatic cells following the introduction of "stemness genes" such as *Oct4*, *c-myc*, *Sox2*, and *Klf4*[10–12]. These 'inducible pluripotent stem cells' (iPSC) overcome the ethical problems associated with ESCs; thus, iPSC biology and its possibilities for clinical applications have been the focus of intensive research. However, although mESC/iPSC have been shown to differentiate into somatic stem cells *in vivo* in chimeric animals, the induction of tissue-specific somatic stem cells from iPS cells remains a challenging problem. One primary reason for this is the difficulty in maintaining iPS-derived stem cells in cell lineages that require rapid cell cycling of their progenitors to maintain cellular homeostasis (such as in the blood, skin, and skeletal muscles). Thus, the use of iPSC to produce functional progenitor cells, or even mature cells, may be most successful when cellular targets have relatively slow intrinsic cycling rates and thus do not require rapid somatic cellular replacement. Recent major advances in iPS-derived cell therapy have been reported in a non-human primate spinal injury model and in a clinical trial of iPS-derived retinal pigment epithelium replacement[13;14].

According to currently accepted stem cell theory, each tissue in the body is maintained by tissue-specific stem cells with the capacity for self-renewal and specific lineage differentiation. During embryonic organogenesis, stem cells differentiate into lineage cells that form specific tissues. These stem cells are maintained in the tissues even during adulthood: for example, cell types such as hair, skin, melanocytes, blood, muscle, intestinal epithelium, and sperm are continuously regenerated by tissue specific stem/progenitor cells. Although the healthy liver does not typically undergo tissue regeneration, if damaged the liver becomes a regenerative organ. Stem/progenitor cells, which have been identified in every tissue/organ, reside in a special microenvironment, called a *niche*, which facilitates the maintenance of self-renewal capacity. Although the brain and nervous system were not previously considered to have regenerative abilities, recent studies have identified stem/

progenitor cells and their niches even in adult animals[15–17]. These cells may play a role in the maintenance of tissue homeostasis and can acquire the ability to produce lineage-specific cells for tissue regeneration following injury.

Recent technological advances have facilitated the identification, isolation, and purification of human somatic stem cells. The hematopoietic stem cell (HSC), the first stem cell to be experimentally proven in humans, resides in the bone marrow and is thus readily accessible for clinical purposes. Blood stem/progenitor cells have a homing ability that enables their migration to and engraftment in the bone marrow of the recipient when administered intravenously, without the need for surgical "implanting" procedures. HSC transplantation has been successfully performed to treat a wide spectrum of hematopoietic disorders and malignancies.

The hematopoietic system is the best *in vivo* example of the somatic stem cell theory. Post-transplantation bioassays have defined HSCs and confirmed their self-renewal and multi-lineage blood cell differentiation capacities. Long term (LT-) HSCs exhibit prolonged engraftment in recipient BM (more than 4 months in mice, 4–8 months in humans) and are secondary transplantable. LT-HSCs sit at the apex of the hematopoietic hierarchy system (Figure) and give rise to short term (ST)- HSCs, or multipotent progenitor cells (MPP), that engraft recipient BM for less than 4 months. ST-HSCs/MPPs differentiate into lymphoid-primed progenitor cells (LMPP) and common myeloid progenitor cells (CMP) in mice, or multilymphoid progenitors (MLPs) and CMP in humans. Murine LMPPs and human MLPs are primarily lymphoid progenitors that produce B and T cells but still retain myeloid potential. The more lineage-specific CMPs give rise to erythrocyte, megakaryocytes, granulocytes, monocytes/macrophages, and dendritic cells. Thus, HSCs produce a wide variety of blood cells and are maintained by self-renewal mechanisms within the hematopoietic BM niche.

Since the discovery of HSCs in umbilical cord blood (CB) and the first successful CB transplantation in a patient with Fanconi anemia in 1989, CB has been widely used for HSC transplantation in addition to BM or mobilized peripheral blood (PB) HSCs[18–20]. In this chapter, we will describe the development of HSCs in in the human embryo/fetus and other stem/progenitor cells found in CB. We will also discuss ongoing and possible clinical applications utilizing CB and related stem cells.

Hematopoietic Stem Cells

Human Embryonic HSC Development in Mice and Humans

The first HSCs are produced during embryogenesis, but are also found in the adult BM niche at steady state. Human cord blood contains proportionately greater numbers of circulating CD34+ HSCs than does the peripheral blood of adults[21].

Developmental hematopoiesis has been well described in mice, an ideal model given a short (19-day) gestation.[22]. The first site of hematopoiesis, the extra-embryonic *yolk sac (YS)* at embryonic day (E) 7.5, consists of mainly large erythroid cells, called *primitive erythrocytes*[23]. Primitive erythrocytes express embryonic-type hemoglobin molecules and

have a large nucleus[24]. Erythroid progenitor cells that express adult type hemoglobin molecules are called *definitive* erythroid progenitor cells and are detected from E8.0 YS together with myeloid progenitors[25]. The progenitors of definitive erythroid cells and myeloid cells are called *erythro-myeloid progenitors* (EMPs) and are produced mainly in the YS during E8 to 10[26]. The first murine HSCs that can reconstitute lethally irradiated adult marrow by transplantation assay are detectable at E11 in the *aorta-gonado-mesonephros (AGM)* region[27;28]. These EMPs and HSCs are all derived from endothelial cells, called *hemogenic endothelial cells (HECs)*[29–32]. The transition from HECs to hematopoietic cells occurs between E7.5 to E11.5[33]. HSCs produced by the HECs in the aortic area migrate into the fetal liver and placenta, where they subsequently undergo a massive expansion[34–36]. HSCs migrate into the spleen and bone marrow at the end of gestation, just before birth, and HSCs ultimately reside in the bone marrow niche to maintain hematopoiesis throughout the life.

Similarly, in humans, hematopoiesis is first observed in the YS as early as embryonic day 18 (presomite stage)[37]. Primitive and definitive hematopoiesis are observed in the YS up to 7 weeks of gestation and are gradually replaced by fetal liver hematopoiesis, which has been initiated by gestational day 30[38;39]. Hematopoietic clusters expressing CD34 and CD45 have been observed in the ventral wall of the dorsal aorta beginning on day 27[40–42]. These clusters rapidly increase in size and can attain several hundreds of cells by day 36. The intra-aortic CD34+ cells express important hematopoietic transcriptional factors including *tal/SCL*, *c-myb*, and *GATA2*, as well as CD143 (angiotensin-converting enzyme), which is known to enrich HSC activity in CB CD34+ cells[43;44]. Studies have shown that NOD/SCID/IL2Rγc^{null} (NSG) mice can be reconstituted with human HSC[45], and active human colony forming activities are detectable in the recipient mouse bone marrow. The first human HSCs shown to reconstitute NSG mice for up to 8 months have been identified in the day 32 AGM region[46]. These AGM-derived HSC are detectable in the peripheral blood of recipient mice 3 months post transplantation. Their numbers gradually increase over time, reaching up to 90% of chimerism by 8 months following transplantation. Human AGM-derived cells also reconstitute secondary recipient mice and display self-renewal capacity (a key measure of stem cell function), generating at least 300 daughter HSCs[46]. HSC in the AGM region express CD34, CD45, VE-cadherin, c-kit, thy-1, and endoglin, but not CD38[47]. Since VE-cadherin is an endothelial specific marker, these observations suggest that human HSCs are derived from HECs as has been observed in murine HSCs. Fetal liver HSCs are first detected on gestational day 42 and express CD34, CD45. VE-cadherin is also initially expressed on these HSCs, although this is lost after 10 weeks of gestation[48].

Circulating CD34+ HSCs are found in both full term and preterm CB[49;50]. The proportions of CD34+ cells in preterm CB are generally higher than in full term CB, although the absolute numbers of CD34+ cells reported has been variable. While preterm CB CD34+ cells exhibit higher colony forming ability than full term CB CD34+ cells[49], preterm CD34+ cells may have lower repopulating ability[48]. The ability of transplanted CD34+ cells to repopulate the bone marrow in patients with severe combined immune deficiency (SCID) has been shown to correlate with the expression level of CXCR4, a surface receptor involved in cellular migration, or homing, to the bone marrow[39]. Thus functional differences

between preterm and term CD34+ cells may be linked to a relative developmental deficiency of CXCR4 in preterm CD34+ cells[49].

Mesenchymal stem cells (MSCs)

Original observations showed that implantation of BM cells (without bone) into non-hematopoietic tissues (such as under skin or peritoneal cavity) induced the development of reticular tissue followed by bone formation that could sustain ectopic hematopoiesis[51–53]. This ectopic bone formation is derived from a non-hematopoietic cell population that forms a clonal fibroblastic colony *in vitro*, the CFU-F[54]. The progeny of CFU-F contribute to bone formation following transplantation and can differentiate into multiple skeletal tissues including bone, cartilage, adipose tissue, and fibroblastic tissue *in vivo*. This rare BM population was first named an *osteogenic stem cell* or a BM stromal stem cell[55;56]. The discovery of this cell type was important in that it identified the presence of a second stem cell population in the BM in addition to HSCs. The currently used term, *mesenchymal stem cell (MSC)*, was first proposed in 1991 based on the capacity to differentiate into cells of the mesenchymal lineage (bone, cartridge, tendon, ligament, BM stroma, adipocytes, dermis, muscle, and connective tissue)[57]. However, the "multipotency" of MSCs remains controversial[56;58]. Furthermore, while MSCs are often referred to as "stem cells", they do not meet strict criteria regarding self-renewal capacity and multilineage potential at the single cell level[55]. A more conservative definition of MSCs (*mesenchymal stromal cells*[59] or skeletal stem/progenitors[60]) include the following: 1) They possess CRU-F that can form fibroblastic colonies *in vitro;* 2) They have the capacity to differentiate into adipocytes, osteocytes, and chondrocytes *in vivo* and *in vitro*; and 3) They support hematopoietic development.

MSCs can be derived from embryonic limbs, postnatal BM, umbilical cord blood and other tissues in mouse and man[51;57;61–63], including the perivascular area or BM sinusoids[64]. Their developmental origins are primarily from mesoderm but they also originate in part from neuroepithelium[65]. MSCs express unique surface antigens including Sto-1, CD271, CD146, but lack hematopoietic and endothelial markers (CD45, CD14, CD11b, CD79, CD19, HLA-DR, CD34, and CD31).

MSC exhibit poor engraftment capacity following intravenous injection, and the small number that do engraft survive for only a short time in the recipient animals[66]. Despite this shortcoming, MSCs may be useful for: 1) Direct cell replacement for tissue regeneration; and 2) Indirect effects on damaged tissue related to MSC secretion of immunosuppressive factors. The therapeutic benefit of MSCs appears to be greatest for the treatment of inflammatory diseases through the release of anti-inflammatory cytokines.

Endothelial progenitors: endothelial colony forming cells (ECFC)

The first putative endothelial progenitors were isolated from human adult PB in 1997 by Asahara *et al.*[67]. The major discovery that endothelial progenitor cells (EPCs) circulate in the peripheral blood led to the concept that these "EPCs" contribute to the repair of vascular injuries. However, this nomenclature was unfortunate, as it has created long-standing confusion regarding the true definition of "EPCs": the cells originally defined as EPCs have

since been designated as hematopoietic cells, not endothelial cells[68]. The term that now most reliably defines circulating endothelial progenitors obtained from human PB or CB is *endothelial colony-forming cell (ECFC)*[69]. ECFCs are strictly defined as endothelial progenitors and are differentiated from "EPCs" based on specific criteria. These include: 1) The *in vitro* ability of cloned cells to form large colonies with high proliferative potential that can be re-cultured to form secondary colonies; 2) The *in vivo* capacity to form capillaries that anastomose with host vessels; 3) The *in vitro* capacity to form tubes with lumens when plated in collagen; 4) Absence of hematopoietic surface markers, but surface expression of other unique markers including CD31, CD146, CD144, CD105, CD34 (partially), KDR, vWF, and lectins; and 5) Lack of phagocytic function. ECFCs or endothelial cells do not have phagocytic function, whereas "EPCs" or macrophages easily phagocytize *E. coli* fragments.

ECFCs are quite rare in CB (2 out of 10^8 CB MNCs); however, their numbers are relatively enriched in CB compared to adult PB. CB-ECFCs have long telomeres and their HPP is also much higher than adult PB-ECFC[69]. While the cells currently designated as EPCs are not true endothelial cells, they share similarities to the recently reported pro-angiogenic $AC133^+CD34^+CD45^{dim}lin^-$ hematopoietic stem/progenitor cells and may contribute to neovascularization in cardiovascular disease or tumor progression[70–72].

iPS and iPS-derived ECFC

Human iPS cells have been established in various human cells. Although CB does not contain truly pluripotent stem cells, CB can be induced into iPS cells when cultured in the presence of defined factors[73;74]. Cord blood iPS cells are hardy: a recent report showed that CB MNCs cryopreserved for over 20 years could still be utilized for HSC transplantation, ECFC isolation and the induction of iPS cells[75]. In addition, a novel culture system to produce ECFCs from human iPS has been established[76]. Human iPS derived-ECFCs display high clonal proliferative ability and have the capacity to form human vessels in mice. Importantly, these pluripotent cells can repair ischemic regions in mouse retina and limb injury models without inducing secondary teratoma formation. Thus, CB is useful not only for its stem cell populations but also for the induction of iPS cells that can be stored for future clinical use.

Stem Cells for the Treatment of Post-Insult Injury in Neonates

Neonates are highly susceptible to inflammatory and/or ischemic insults, particularly to critical organs such as the brain and lungs; this risk is considerably higher in the most immature, preterm infants[77–79]. The damaging and often permanent effects related to these newborn insults are associated with high economic and societal costs, while the personal suffering of the afflicted and their families is incalculable[80;81]. Thus, the successful prevention or treatment of insult-related injury is of utmost and immediate importance.

Neonatal injury and its inherent complications have been intensively studied for many years. Investigations in relevant animal models and human studies have advanced our understanding of the underlying mechanisms; however, treatments to prevent or to arrest injury as a result of these insults in many cases have been disappointing, until recently. A

growing body of evidence and exciting new discoveries indicate the potential (and in some cases, actual) regenerative role of SCT in the treatment of neonatal injury, as briefly reviewed below.

Brain injury and SCT

Hypoxic-ischemic encephalopathy—Studies in animal models have been critical to defining the mechanisms underlying post-insult brain injury. These models have been based on approaches that focus on either cellular/molecular mechanisms or that recapitulate the physiologic events that produce injury; these have been recently elegantly reviewed[82]. However, existing evidence has been distilled from studies using a spectrum of animal models and SCT approaches, primarily involving human amnion epithelial-derived cells (hAECs), MSC, whole cord blood and neural stem cells. Thus, the reparative benefits of SCT for post-insult brain injury and the specific cells involved remain unclearly defined (reviewed in[83]).

Umbilical cord blood is a repository of a plethora of stem cell types, including those of hematopoietic, endothelial and mesenchymal origin, as was discussed in the first part of this review. Rodent models of neonatal hypoxic-ischemic brain injury have exhibited structural and behavioral improvements following transplantation with human cord blood cells, including measurable improvements in cognition{de Paula S., 2012 19297 /id;Wasielewski, 2012 20076 /id;Geissler, 2011 20087 /id}. However, the specific stem cell type(s) or cell combinations in cord blood that confer therapeutic properties have not been well defined. The underlying mechanisms are also unclear; evidence of poor engraftment in animals that respond positively to SCT suggest that the ameliorative effects are not due to the regenerative capabilities of the administered stem cells[87]. A relationship has been established between neuroprotection and indirect (paracrine and trophic) modulatory effects of administered stem cells, including MSCs and hAECs, on inflammatory and excitotoxic neural responses[88;89]. Administration of hAECs to sheep fetuses was also shown to confer protection from inflammation-induced brain injury[90].

Studies of cord blood SCT in humans, while sparse, are increasing. In a recently reported prospective trial, 23 infants with hypoxic-ischemic encephalopathy received both head cooling and autologous cord blood transfusion within the first 72 hours of life[91]. The authors concluded that this form of SCT was both safe and feasible even in outborn infants transferred to a tertiary care hospital. However, no firm conclusions could be made regarding hospital and developmental outcomes or 1-year survival. In a feasibility pilot study, the transfusion of autologous cord blood from private cord blood banks to young children with neurologic disorders was found to be safe[92]. In a Korean study of 96 infants and children with cerebral palsy, subjects who received matched allogeneic cord blood cells with erythropoietin fared better developmentally six months later than did their counterparts given erythropoietin only or placebo[93]. Importantly, this study highlights the potential therapeutic utility of banked allogeneic donor cord blood cells in SCT of brain injury.

Neonatal stroke—Stroke is a primarily ischemic event that occurs in the fetal or neonatal periods and involves ischemia of cerebral arteries or periventricular venous infarction[94].

Strokes in the perinatal period commonly (60% of cases) result in neurologic deficits, with hemiplegic cerebral palsy being a frequent complication. A variety of preclinical studies have shown potential therapeutic value of stem cell populations derived from human umbilical CB in limiting injury and in promoting functional recovery. In rodent stroke models, the administration of neural stem cells lead to glial and neuronal differentiation at sites of injury, while transplanted MSCs were indirectly beneficial by inducing the release of neuroprotective trophic factors that dampened inflammation[95;96]. Human CB-derived AC133+ EPCs limited infarct size and shortened the resolution period in a rat stroke model[97]. Stem cell types in addition to those derived from CB may also be of value. The administration of amniotic fluid-derived stem cells to adult rats with ischemic stroke also resulted in significant functional recovery[98]. However, the most beneficial stem cell type for the treatment of stroke remains unclear. Transplantation with the broader array of stem cells contained in human CD34+ cells bestowed a limited benefit in one rodent stroke model, while another study showed greater therapeutic effect and less inflammation in animals receiving CB mononuclear cells compared to CB MSCs[99;100]. While the potential therapeutic utility of SCT in neonates with stroke is supported by preclinical studies, however its actual utility in human neonates, while promising, remains to be defined[101].

Lung injury and SCT

Extremely preterm infants are at high risk for numerous long-term complications, of which bronchopulmonary dysplasia (BPD) is the most common[102]. The “new” BPD is associated with lung growth arrest as well as abnormal vascularization and fibrosis, and it can result in disabling lung abnormalities that persist into adulthood[79]. Studies in neonatal animal models of BPD have shown that transplantation with MSC or soluble MSC-derived proteins (the MSC “secretome”) can modulate BPD by dampening inflammatory processes[96;103–105]. In a recently reported phase I dose-escalation trial, a small group of extremely preterm infants who received intra-tracheal autologous MSC had diminished BPD severity and lowered inflammatory cytokine levels in tracheal aspirates compared to historical controls[106]. Importantly, MSC treatment was clinically well tolerated in these tiny babies and was not associated with discernable short-term safety issues. The potential benefits of cord blood MSCs have stimulated numerous ongoing clinical trials addressing their use for the treatment of diverse disorders in adults and several in preterm infants.

Intestinal injury and SCT

Necrotizing enterocolitis (NEC), an intestinal inflammatory disorder with infectious components, is a common and potentially devastating complication of prematurity[107]. The etiology of NEC is multifactorial and includes ischemia-reperfusion injury, disturbances of the intestinal microbiome and prior inflammatory exposure. The potential role of SCT in the treatment of neonatal NEC has only recently been addressed. In an *in vivo* neonatal rat model of NEC, intraperitoneal administration of bone-marrow derived MSCs was associated with attenuated histologic intestinal injury, improved weight gain, and decreased clinical illness scores[108]. MSC homing to intestinal tissue was enhanced in the pups with NEC compared to normal controls, suggesting a potentiating role for inflammation in the engraftment of MSC. In another study, neonatal rats with NEC that were treated with amniotic fluid stem cells showed improved gut structure, survival and reduced inflammatory

mechanisms mediated via COX-2[109]. Despite these encouraging preclinical data, a role for SCT in the treatment of NEC in human neonates has not been reported to date.

Utility of Neonatal SCT: General Considerations

A number of critical questions remain to be answered through well-designed pre-clinical large animal models and human clinical trials before the use of umbilical CB or specific stem cells afford reasonable therapeutic options. One important issue is that of the optimal timing of SCT administration in the context of the injury. Studies in infants with brain injury have shown a secondary post-injury period during which inflammatory and excitatory mechanisms become pronounced, thus the time between the initial insult and this later phase may be the ideal window to institute SCT as a therapeutic measure[110]. Conversely, a Korean study showed benefit of SCT in children with cerebral palsy, even in those who were 10 years of age[111], which suggests a possible benefit despite long-standing neurologic injury.

Another key issue to be addressed is the identification of the ideal stem cell source for a specific type of tissue injury. As detailed earlier in this review, umbilical cord blood contains numerous stem cell types, including those of hematopoietic, endothelial, and mesenchymal origins. However, it remains unclear if and how the perinatal factors contributing to neonatal hypoxic-ischemic encephalopathy or other injury could potentially influence the functionality and intrinsic properties of the cord blood stem cells themselves[112].

The role of specific stem cell types in various target organs also remains incompletely defined. Mesenchymal stem cells (MSC) derived from developing humans exhibit a high degree of mesodermal pluripotency (the capacity to differentiate into multiple cell types); in addition, these MSC are associated with a low induction of immune responses in the recipient and exhibit anti-inflammatory properties[96;113]. Another type of cell with pluripotent properties is the hAEC[114]. Like MSCs, hAECs are anti-inflammatory and appear to be immunologically well-tolerated[115;116]. Studies in fetal sheep showed that AEDC administration was protective against brain inflammation, including periventricular white matter injury[90]. As also observed with MSCs, the beneficial effect of hAECs may be primarily related to the release of soluble protective factors[87].

In addition to the optimal stem cell type and timing of administration necessary for therapeutic efficacy, other questions that remain to be answered include: the most ideal stem cell sources (autologous *versus* allogeneic, cord blood *versus* isolated stem cells, primary cells *versus* derived or genetically modified cells), host tolerance, and safety, among others[110;117]. While short-term safety may be acceptable, as suggested by the very small number of recent human studies, long-term effects remain unknown. This latter point may be of particular importance to very preterm infants who are still undergoing developmental maturation, including of the immune and hematopoietic systems. Another critical safety feature to be defined involves the potential tumorgenicity or cancerous conversion of the transplanted stem cells, a question that remains enigmatic.

Summary

True stem cells or cells with pluripotent properties are found in a variety of tissues and organs. Umbilical cord blood can provide a spectrum of stem or pluripotent progenitor cells, many of which have a greater potential for proliferation (although not necessarily engraftment) compared to similar cells mobilized from the bone marrow into the peripheral blood of adults. Preclinical studies have shown a therapeutic benefit of SCT in perinatal and neonatal injuries, including those involving the brain, lungs and intestines. The very few human studies to date suggest short-term safety of MSCs or cord blood (both autologous and allogeneic) SCT and have variably shown measurable improvements in functional or inflammatory parameters. However, the therapeutic mechanisms remain incompletely defined, and the optimal usage of SCT for a particular type of injury is also unclear. Thus, despite its exciting potential for currently untreatable neonatal disorders, extensive studies in both preclinical models and in humans will be necessary before SCT becomes an accepted form of therapy. Although still quite limited relative to studies in adults, an increasing number of human trials now address these issues in neonates (https://ClinicalTrials.gov).

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Key Points

- Umbilical cord blood contains a plethora of stem cells and multipotent progenitor cells.
- In preclinical animal models, transplantation with cord blood or specific stem-like cells can limit brain and lung injury and/or preserve or restore function in part through anti-inflammatory mechanisms.
- The small number of human studies to date suggests the short-term safety of cord blood-derived stem cells, however additional preclinical and human studies are needed to establish therapeutic efficacy and long-term safety.

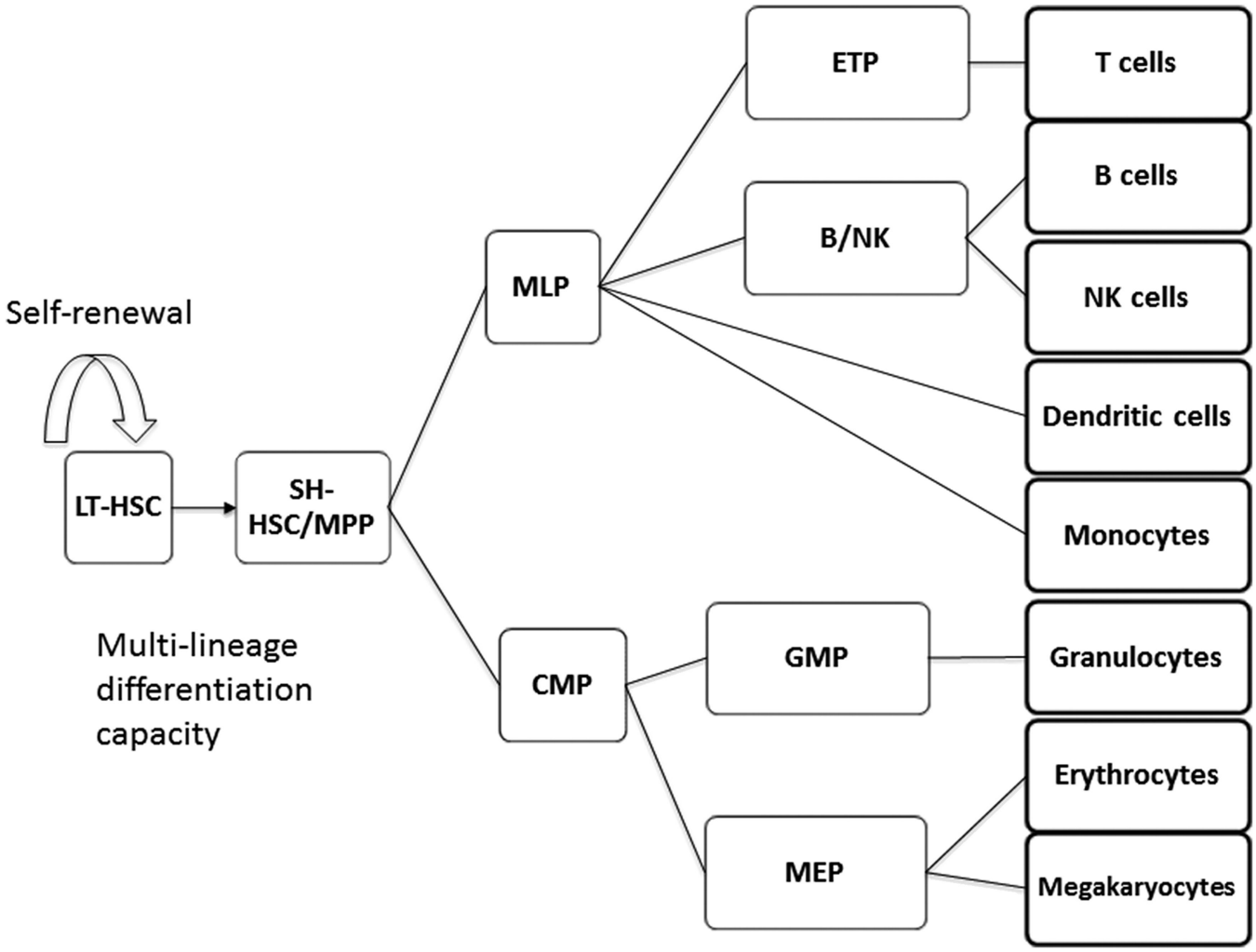

Figure 1. Hematopoietic hierarchy system

Long-term hematopoietic stem cells (Lt-HSCs) sit on the apex of the hematopoietic hierarchy system. LT-HSCs that reside in the bone marrow hematopoietic niche maintain self-renewal and multi-lineage differentiation capacity through asymmetric cell division. SH-HSC: short-term hematopoietic stem cell, MPP: multipotent progenitor cell, MLP: multilymphoid progenitor cell, CMP: common myeloid progenitor cell, ETP: earliest T lymphoid progenitor cell, GMP: granulocyte-macrophage progenitor cell, MEP: megakaryocyte-erythroid progenitor cell.