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The Therapeutic Potential of Stem Cells in Umbilical Cord and Umbilical Cord Blood

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INTRODUCTION

Haemopoietic stem cell transplantation (HSCT) is a curative therapy for severe haematological disorders. It was first carried out successfully ~50 years ago. With technological advances, HSCT has expanded rapidly over the past 20 years.[1,2] Current indications for HSCT include leukaemias, lymphomas, solid tumours (e.g. neuroblastomas), severe combined immunodeficiencies, inborn errors of metabolism, autoimmune diseases and severe anaemias.[1-3] HSCT is now provided to ~70,000 patients p.a. worldwide. In the UK, approximately 3,000 HSC transplants are performed p.a. (www.bsbmt.com), contributing to ~25,000 p.a. across Europe.[1-4] Of those HSCT provided worldwide, ~70-80% have autologous or related allogeneic HSCT. The remainder have unrelated HSCT, of which almost 20% are sourced from unrelated umbilical cord blood (UCB) donations in the USA and 50% in Japan.[4] Despite significant advances, overall survival following HSCT can vary because of disease relapse, engraftment failure, infections and Graft versus Host Disease (GvHD).[5,6]
In this review, we describe the current use, advantages and limitations of UCB for HSCT, principally concentrating on unrelated allogeneic UCB units. However, UCB and the umbilical cord (UC) also contain other stem/progenitor cells (e.g. mesenchymal stem cells (MSC)) and hence we extend our discussions to these describing their potential therapeutic use in HSCT and regenerative medicine.

Key Words: umbilical cord blood, stem cells, mesenchymal stem cells, GvHD, infections, engraftment, expansion, tissue repair, immunomodulation

HAEMOPOIETIC STEM CELLS (HSC) FROM UMBILICAL CORD BLOOD FOR HSC TRANSPLANTATION

UCB was first successfully transplanted in 1988 in a child with Fanconi's anaemia using an HLA-identical sibling UCB.[7] It is now well accepted as an alternative source of allogeneic HSC for certain disease indications.[3-17] As well as unrelated donations, directed allogeneic donations from family members, especially when they provide a disease free identical HLA-matched UCB donation through pre-natal HLA typing and genetic screening, are most often used for the treatment of siblings suffering from such inherited isorders as haemoglobinopathies.[11-15] The resulting matched directed sibling donor transplants generally demonstrate less GvHD then matched unrelated donations.[11-15]

Advantages of UCB over BM and peripheral blood stem cells (PBSC) include less stringent HLA matches, reduced GvHD, lack of donor attrition, urgent provision and ready accessibility of viral pathogen free and HLA typed HSC, especially for those from ethnic minority groups where finding matched HSCs can be difficult, although high cell dose and HLA matching are impor-

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tant indicators of outcome.[13-18] However, engraftment of UCB HSCs is inefficient, with each UCB unit containing limited HSC numbers, delays in haematological reconstitution and increased risks of viral infections post HSCT with UCB. Other disadvantages include the lack of donor lymphocytes for enhancing a graft versus malignancy effect or to combat infections and in the case of tandem transplants, the lack of a back-up HSC donation. With HSCT increasing worldwide, with predicted doubling of the usage of UCB in HSCT in adults and with significant technological advances, the trend now is for more personalised treatments to fit patient need.[3,4,15-17] Thus, there is still a need to increase the efficacy of the HSCs available for HSCT by reducing engraftment failure rates through a better understanding of the control of stem cell fate, improving homing and engraftment, identifying and targeting the malignancy initiating stem-like cells and regulating the immune response to control GvHD and viral infections which contribute significantly to graft failure and poor survival.

ADVANCES IN UCB HSC TRANSPLANTATION

HLA matching and cell dose

HLA matching is important to the outcome of allogeneic HSCT, with GvHD being a serious consequence of mismatches between donor and recipient in the unrelated allogeneic setting especially with BM and PBSC where 10/10 HLA allele matching is sought at 5 loci – HLA-A, -B, -C, -DR and –DQ.[17] Since HLA matching is considered less important in UCB HSCTs, more mismatched (at 1-2 loci) UCB HSCT have been performed, but limited cell dosages in such single UCB units can further contribute to delays in engraftment and subsequent effects on early survival post transplant. UCB units are most often selected for 3 HLA loci based on high resolution matching at the allelic level for HLA-DRB1 and at low-intermediate HLA-A and –B resolution. Studies have indicated that to achieve >50% survival, cell dosages of $>2.5x10^7$ and $>5x10^7$ per kg recipient body weight were required for 5/6 and 4/6 mismatched UCB grafts respectively.[17] Conclusions from 1,061 single UCB myeloablative transplants for patients with leukaemia or myelodysplasia (given adequate TNC (total nucleated cells) were i) faster neutrophil engraftment with HLA-matched grafts; ii) no difference in time to neutrophil engraftment between 5/6 or 4/6 HLA-mismatched grafts; iii) there was a lower incidence of grade 3-4 acute GvHD in matched grafts; and iv) lower transplant related mortality (TRM) correlated with higher pre-cryopreservation TNC and better HLA matching, without increased relapse rates.[17] Other studies[5,6] revealed that, in children receiving 4/6 and 5/6 mismatched UCB transplants for leukaemia, infusion of $>3x10^7$ TNC per kg recipient body weight provided similar outcomes to those receiving matched BM.

As cell dosage can partially overcome the adverse effects of HLA mismatch, Smith and Wagner[8] have recently defined the adequacy of UCB cell dosage for HSCT as a TNC/kg recipient body weight of $>3\times10^7$ for 6/6, $>4\times10^7$ for 5/6 and $>5\times10^7$ for 4/6 HLA matched cord blood units. Based on these cell doses, the following recommendations were made recently[8,9] for sourcing cells for unrelated allogeneic HSCT: (i) selection of cells from UCB, BM or PBSC based on patient need as judged by the transplant physician treating the patient; (ii) for malignant disease, a 6/6 HLA matched UCB with an adequate cell dose (as above) for both children and adults as the first choice, with an 8/8 HLA matched unrelated BM or PBSC harvest or a 5/6 or 4/6 HLA matched UCB as the second choice but the decision would be based on cell dose, the urgent need for a transplant, and the future requirements for tandem transplants or donor lymphocyte infusions; and (iii) for non-malignant disorders, there was no definite recommendation although the gold standard was cited as an 8/8 HLA BM for both children and adults, or PBSC harvest in adults, with the next choice suggested as an adequate dose of 6/6 or 5/6 HLA matched UCB unit. Eurocord data have recently suggested that, for non malignant conditions, HLA disparity affects engraftment, GvHD, survival and TRM and have recommended a cell dose of $>3.5x10^7$ TNC per kg recipient body weight when treating such patients.[17 and references therein] Additionally, some investigators have indicated that CD34 dose is an important predictor of UCB HSCT outcome and time to neutrophil recovery, but this is not often used as one of the routine selection criteria.[14 and references therein]

Unlike BM HSCT, few data exist on the positive effects of high-resolution HLA matching in the UCB setting,[19,20] although recent studies[21] suggest faster neutrophil, but not platelet, recovery with Class I HLA-B (but not Cw) matching of single or double UCB units. It has been hypothesised that HLA-B may act as a target for NK cell KIR receptors[22-24] and that such mismatching results in selective killing of the donor UCB cells. Additionally, HLA Class II (DR) mismatching in the double UCB HSCT setting correlates with grade II-IV acute GvHD.[19-24]

Improving UCB HSC engraftment

Limited cell numbers have presented a significant problem in unrelated allogeneic UCB HSCT in adults. The most obvious way to enhance haematological reconstitution, determined as the time to peripheral blood neutrophil and platelet recovery, is to increase the numbers of UCB haemopoietic stem/progenitor cells transplanted. For unrelated UCB allogeneic transplants, strategies to improve engraftment include enhancing the homing mechanisms and fate determination in the BM niche, transplantation of two UCB units, direct injection of HSC into the BM and ex vivo expansion of UCB HSC using exogenous cytokines. The use of double unrelated UCB HSCT in adults has extended their use in patients up to 75 years of age.[14,25] However, even with 2 UCB HSCT into one recipient, one UCB often engrafts long term in preference to the other.[14,26] These new transplant approaches have complemented the increased clinical experience in UCB HSCT in terms of patient conditioning, time of UCB administration, disease type and status etc and an improved understanding the importance of UCB quality.[14,27,28]

Ex vivo expansion of UCB HSC has been attempted with various cytokine cocktails, chimaeric cytokine/cytokine receptors or soluble transcription factors (e.g. TPO, FLT3L, SCF, IL6Rα, Notch ligands, AngptLP, HoxB4).[14,29-38] Many of these have not significantly or safely expanded HSCs without their differentiation. For example, a recent phase I myeloablative double UCB trial using ex vivo Notch-ligand treated UCB HSC showed enhanced neutrophil but not platelet recovery and insignificant expansion of long-term repopulating HSCs.[4,38] Although initially promising and although this technique may reduce the severity of GvHD at least with single UCB HSCTs, intrabone injections do not appear to have improved engraftment outcomes in the double transplant setting.[14,39] Another approach has been to supplement single or double UCB transplants with mobilised peripheral blood $CD34^+$ cells or third party mesenchymal stem/stromal cells (MSCs).[14,40,41]

MSCs in UCB and UC. Can these benefit UCB HSCT and tissue repair?

MSCs, which are found in the BM, placenta, UCB and the UC, are thought to suppress GvHD following HSCT and may enhance HSC engraftment.[14,40-42] They may also contribute directly to tissue repair (e.g. of the vasculature, bone, cartilage) or act in a paracrine, endocrine or anti-inflammatory manner (e.g. by promoting revascularisation or the proliferation of endogenous stem cells, limiting scarring or apoptosis, or modulating tissue remodelling, without necessarily replacing the damaged tissue itself).[43-46 and references therein] Other stem/progenitor cell types including endothelial progenitors,[47,48] multipotent USSC (unrestricted somatic stem cells),[49] and VSEL (very small embryonic-like) stem cells have also been described in UCB.[50] MSCs represent a special case because their therapeutic potential in immunomodulation during HSCT and for tissue repair has been well described, at least when sourced from BM.[45,51] The remainder of this review will concentrate on MSCs especially those derived from UC.

Definition of MSCs

BM MSCs were the first characterised as plastic adherent fibroblastoid-like cells expressing CD90, CD73 and CD105, but not CD14, CD11b, CD79, CD34, CD45 or HLA-DR, with the ability to generate clonogenic fibroblastoid colony forming umits (CFU-F), and to at least differentiate into adipogenic, chondrogenic and osteogenic lineages *in vitro*.[52,53 and references therein] Sarugaser et al.[54] have recently defined the most primitive MSCs more stringently as those multipotent cells with clonal single cell derived self-renewing activity and the ability to generate at least 5 lineages, viz. fat, cartilage, bone, muscle, and fibroblastic lineages (tendon, ligament and stromal). The BM stromal cells[55] can for example support haemopoiesis or suppress GvHD.[14,40,41,42,45] Despite this, the MSC terminology has generally been loosely used to encompass both self-renewing stem cells with the ability to form multiple lineages and heterogenous cultures of cells with a fibroblastic phenotype and with differing capacities to generate multiple lineages, particularly fat, bone and cartilage, and often without an explicit demonstration of their self-renewal potential.[52] Here, we will use the term MSC to refer to both the mesenchymal stem cells and their progeny often called mesenchymal stromal cells, but will attempt to distinguish these cells by their known functional capacities.

MSC tissue distribution

Originally identified in BM where they occur at a clonogenic frequency of 1 in 10^4-10^5 mononuclear cells, MSCs with multipotent properties at least *in vitro* are also found in the fetal circulation being particularly prevalent in the first trimester of pregnancy, in fetal and adult tissues, UC and mid-gestation amniotic fluid.[56-68] It is generally accepted that MSCs from earlier stages of ontogeny have a higher proliferative ability and greater functional capacities. Recently, the perivascular niche has been suggested as the potential site of origin of MSCs

in many organs[56,57] (although this is not universally accepted[60]) and it has been proposed that under homeostatic conditions, although multipotent, such perivascular cells (PVCs) by default generate stromal cells for the organ of origin rather than multiple lineages. An example is the adventitial reticular cells or CD146+ osteoprogenitor cells which are closely associated with the sinusoidal endothelium in the BM where their main purpose is to regulate haemopoiesis.[68] Since only ~10-65% of UCB units generate MSCs in culture[69] and since MSCs from UCB and UC may share a common UC perivascular origin,[54,70] the UC has been examined as an alternative non-invasive source of MSCs of consistent donor age. Furthermore, many of the standards that regulate the collection and banking of UCB for HSCT also translate into the collection of the UC.

MSCs from the UC – Wharton's jelly versus perivascular cells

The UC at term contains two arteries and a vein surrounded by a connective tissue matrix or Wharton's jelly.[71] The vein has been generally used to source UC endothelial cells,[47,48] while Wharton's jelly and UC PVCs have been the main source of UC MSCs.[70-77]

The isolation and characteristics of Wharton's jelly MSCs have been reviewed recently.[71 and references therein] Isolation methods include i) removal of UC vessels before the Wharton's jelly is taken and digested enzymatically with either collagenase/trypsin or hyaluronidse/collgenase/trypsin before culture, ii) by generating MSCs from explants of Wharton's jelly and amniotic membrane without enzymatic digestion and iii) by cryopreservation of 1cm segments of Wharton's jelly in heat inactivated autologous UCB plasma containing 10% DMSO prior to subsequent culture.[64,69,71,72,74,76] As a whole cell population, Wharton's jelly MSCs share some but not all characteristics with BM MSCs. They resemble BM MSCs in their expression of CD90, CD105, CD73, CD13, CD29, CD10, CD13, CD49e, CD51, CD166, CD44 and HLA-A,-B, -C and –G, but lack of expression of CD45, CD14, CD56, CD31 and CD34 and are reported to be HLA DR+.[71,72,76] In our own studies, we detected CD146 on almost 40% of UC PVC but not of the majority of Wharton's jelly MSCs.[75]

A major issue in comparing MSCs from different tissues is in defining their relative functionality and their side-by-side ability to differentiate, to modulate immune and inflammatory responses, to support haemopoiesis or vasculogenesis, and to self-renew.[60] Wharton's jelly MSCs have been reported to form osteoblasts, chondrocytes, adipocytes, cardiomyocytes, hepatocytes, pancreatic, endothelial and neural like cells, to support haemopoiesis and to modulate immune responses.[42,44,64,66,69,71,72,74-80 and references therein] Reports are conflicting and some studies suggest that Wharton's jelly MSCs more closely resemble UCB MSCs than BM MSCs in their reduced ability to form fat cells, and have less potential for osteogenic differentiation as assessed both by side-by-side *in vitro* differentiation and global trancriptome profiling and for chondrocytic differentiation than BM MSCs.[75,76,80] However, Wharton's jelly MSCs appear to retain the ability to support HSC/HPC and ES cell expansion *in vitro* and for immunomodulation.[71,74,76-78] Although Wharton's jelly MSCs have been reported to form cells with myogenic, neural and cardiac muscle phenotypes *in vitro*, it is not universally accepted that these cells are functional in terms of their ability to replace damaged neurons or cardiac muscle. Like BM MSCs, they may promote such tissue repair through paracrine, endocrine or anti-inflammatory mechanisms.[45,60] To add to the complexity, Karahuseyinglu et al.[81] have described Type I and II Wharton's jelly MSCs, which differ in their ability to differentiate into particular lineages, while Hoynowski et al.[82] have identified a subset of Wharton's jelly MSCs which express the so-called pluripotent markers, SSEA-4 and TRA-1-60. Wharton's jelly MSCs can be expanded for >15 passages and possess greater doubling times than BM MSCs.[71,76] While many researchers culture MSCs from the UC prior to analysing them functionally or phenotypically, a great deal of effort has recently been directed into identifying the regions of the UC which contain more primitive MSCs prior to culture.

Where are the MSCs located in the UC?

Cellular content of UC segments have been examined using specific biomarkers both *in situ* and after isolation and culture, with the particular aim of identifying and isolating the more primitive MSCs with stem-like characteristics. Schugar et al.[70] examined the distribution of cells expressing CD44, CD105, CD73 and CD90 in the UC vasculature and Wharton's jelly at the time of isolation and devised a method for the generation of large numbers of such cells. They estimated that the UC segments (average weight 40g) contained ~1.1×10^7 cells/g, and ~5.3×10^5 cells could be isolated per gram after UC digestion. They predicted an entire UC would contain as many as 5×10^8 cells and demonstrated that UC dissection (without the removal of vessels) followed by collagenase digestion consistently generated higher levels of CD146+(40-50%)HLA-class II negative MSCs which

could be enriched for CD146+ cells by flow cytometry. They demonstrated that i) EGM2 medium enhanced the growth rates of the UC MSC allowing some to reach 55 population doubling with a population doubling time of 24h, and ii) maintained phenotypic stability. In other reports where CD105+ explanted UC MSC reached 30 population doubling with population doubling times of ~38h.[71,76,83 and references therein] These differences may reflect the isolation and culture conditions used, as well as the UC location of the MSC. In contrast, mechanical disruption, explant culture and dispase digestion generated CD144+CD146+ endothelial cells.[71,76]

It has more recently been hypothesised that MSCs are derived from CD146+ NG2+ PDGF-Rβ+ ALP+CD34-CD45-vWF-CD144- PVCs expressing α-smooth-muscle-actin,[54,70,73] and hence can be found in most tissues. UC PVCs also express CD44-v3 as defined by the 3G5 antibody, a marker on BM MSCs.[54,73,84] Montemurro et al.[85] examined the distribution of such cells in UC Wharton's jelly, veins, arteries and microvessels preterm (23-32 weeks of gestation-fetal UC), and at term. CD146+ α-smooth-muscle-actin+ PVC cells were numerous in the arteries but not in the vein or Wharton's jelly, the latter containing CD105+ α-smooth-muscle actin+CD146- cells but no cells with endothelial phenotypes. The percentage of CD146+ α-smooth-muscle-actin+ PVC cells was higher preterm (2.5% in preterm and 0.15% in term UCs). The UCs were dissected to expose the Wharton's jelly, vein and two arteries, digested with collagenase and the cells cultured first in EGM2 medium on gelatin and then in high glucose DMEM with 20% FCS. When harvested, UC PVCs occur at a frequency of 1:300 and when cultured have a clonogenic frequency of >1:3. The preterm cultured PVCs (p3) expressed SSEA-4, low Oct-4 and Runx1, but not Rex1, Sox2, Myo-D, Myf 5, CD31, CD45, CD34 or CD144. *In vitro*, these cells were shown to differentiate into the 3 lineages measured, viz. fat, bone and myogenic cells. Furthermore, in culture a UC PVC subset did not express HLA Class I or II and this may have important implications for allogeneic cell based therapies.[54,85] Their ability to migrate towards damaged lung tissue in an *in vivo* model led Montemurro et al.[85] to suggest that preterm autologous UC PVC may be therapeutically important in treating bronchopulmonary dysplasia in premature infants.

Is there a hierarchy of UC MSCs?

Many studies do not examine the capacity of MSCs to self-renew and differentiate into the 5 functional lineages (quinti-potential).[54] Sarugaser et al.[54] addressed this issue by using clonal single cell analyses to define multipotent MSC subsets derived from UC PVCs or CFUMACOF (colony forming units with muscle, adipocytic, chondrogenic, osteogenic and fibroblastoid potential) which can generate daughter cells *in vitro* with the capacity to differentiate into these same 5 lineages. They propose a hierarchy of MSCs reminiscent of the haemopoietic lineage with the self-renewing CFUMACOF generating self-renewing progenitors which gradually lose their capacity to differentiate (first their myogenic ability, and subsequently adipogenic, chondrogenic and finally osteogenic lineages) eventually giving rise to the myofibroblast. This contrasts with other hypothesised hierarchies,[86, 87] where the default lineage was the osteogenic lineage with multipotent MSCs giving rise to bipotent CFU-OA or CFU-OC. Whichever hypothesis is correct, it must be remembered that MSCs from different sources may have different potentials and it will be important to define MSC subsets and to understand the molecular mechanisms that regulate their hierarchical fate decisions[60] so that MSCs can be optimally expanded and directed into the appropriate lineage for tissue repair or for modulating the immune and inflammatory responses.

Are UC MSC functional in vivo?

This is key and there are various clinical conditions for which MSCs may have potential therapeutic benefits, yet results of clinical trials using BM MSCs are mixed and the mechanisms of their effectiveness are not fully understood. These trials, which have slightly more often (>60%) used allogeneic rather than autologous MSCs, include treating GvHD, SLE, diabetes, bone and joint injuries, cardiovascular diseases, lung, skin and liver diseases/injuries, stroke, spinal cord and brain injury and Crohn's disease.[45 and references therein].

While some trials depend on MSCs regenerating damaged tissues (e.g. bone, cartilage, tendons etc), others rely on MSC immunomodulatory or anti-inflammatory mechanisms. One example of the latter is the European phase I/II clinical trial using allogeneic MSCs to treat GvHD. This showed significant effects in over 50% of patients with steroid refractory GvHD.[88] This contrasts with an international phase III clinical trial led by Osiris Therapeutics where clinical endpoints were not reached.[89] Others are the BOOST and Osiris Prochymal trials for acute myocardial infarction (AMI), which appear to limit scarring and improve left ventricular ejection fraction at least shortly after treatment, but which may not be effective over the longer term.[45 and references therein] Lee et al.[46] have demonstrated in an animal model that upon systemic

delivery, many MSCs lodge in the lung where they secrete anti-inflammatory factors, e.g. TSG-6, which may indirectly prevent further cardiac damage. Our studies have suggested that autologous BM MSCs can remain in the heart in rodent models of AMI, but decrease in number over time and do not significantly differentiate into cardiomyocytes.[75,91-93]

Although clinical translation of novel therapeutics is associated with risks of failure, successful translation, as illustrated earlier by gradual improvements in UCB HSCTs over the past 20 years, takes time but has the potential to revolutionise medical care. A notable recent success has been the transplantation of a tissue engineered decellularised trachea populated with autologous BM MSCs (which form cartilage to mechanically strengthen the graft) and epithelial cells in a patient with TB.[94] This approach is being extended to other tissues.[95-98]

The therapeutic use of UC MSCs, whether from Wharton's jelly or UC PVCs, remains to be tested fully if they are to substitute for BM MSCs.[60,98,99] These cells can be sourced non-invasively but may be immunogenic under certain circumstances as described.[100] They may retain their immunomodulatory or differentiation specific functions. What is elusive and still a challenge is to robustly define the optimal cell source which may be specific for each treatment strategy, as well as cell safety, dosage, immunogenicity, the best route of delivery and the types of patients who would benefit most.[60]

CONCLUSIONS

The key points from this review are:

* UCB and UC contain a variety of stem/progenitor cells including HSCs and MSCs
* It has taken ~20 years for UCB to become an established source of HSCs for HSCT in both children and adults and its usage continues to be optimised
* MSCs are found in the perivascular region and Wharton's jelly of UC, yet the best therapeutic source remains a matter of debate. If they are biologically equivalent to BM MSC in their immunomodulatory or tissue repair abilities, then they could provide an abundant, non-invasive, ethically acceptable supply of cells that could be banked for therapeutic use.
* Robust comparisons of the best source and subset of MSCs are necessary to ensure product quality, safety and efficacy in clinical trials related to HSCT and regenerative medicine.
* Elucidation of the mechanisms by which MSCs exert their beneficial effects is essential to optimising therapeutic benefits.

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