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EXPERT OPINION

Use of umbilical cord and cord blood-derived stem cells for tissue repair and regeneration

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Introduction: Potential use of umbilical cord (UC) is one of the most exciting frontiers in medicine for repairing damaged tissues. UC and cord blood-derived stem cells are the world's largest potential sources of stem cells. UC contains a mixture of stem and progenitor cells at different lineage commitment stages and UC has been verified as a candidate for cell-based therapies and tissue engineering applications due to the capability of these cells for extensive self-renewal and multi-lineage character in differentiation potential.
Areas covered: UC-based repair or regeneration of organs (i.e., heart, nerve, skin, etc.) is a high-priority research worldwide.
Expert opinion: The aim of this review is to summarize the knowledge about UC with main focus on its applications for tissue repair and regeneration.

Keywords: *in vivo*, stem cells, tissue repair and regeneration, umbilical cord

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1. Introduction

Successful progress in discovering the therapeutic potential of cells raised great hope among both biomedical scientists and general populations [1,2]. We surveyed the ISI Web of Science operated by Thomson Reuters for English language papers with regard to 'Stem cells', 'Adult stem cells', 'Embryonic stem (ES) cells', 'Umbilical cord stem cells (UC-SCs)', 'Bone marrow stem cells', 'Umbilical cord (UC) and UC-SCs' and 'Wharton's jelly'. The leading types of published papers were original articles followed by titles or abstracts. When a title or abstract could not be discarded with certainty, the full text of the article was acquired. Each experimental study was independently analyzed in order to grade the quality of the study design. For each eligible study, two reviewers extracted all available and relevant data for the experimental groups. The number of annual publications from 2004 to 2012 revealed that the number of these papers dramatically rose during these years (**Figure 1A and B**). The relatively high frequency of ES cell studies is also notable. The recently discovered UC-SCs were also studied by some researchers. As expected, regarding the developmental stage, the majority of involved studies were about adult stem cells.

By reviewing 270,000 published articles regarding stem cells, adult stem cells (23,650 articles, about 40%), bone marrow mesenchymal stem cells (MSCs) (> 50% from adult stem cells) were found to be the most common cell type used. The number of published articles infield regarding bone marrow stem cells have declined in recent years from 2000 to 2012 (**Figure 1C**), but researches infield of embryonic (from 18.5% during 2000 – 2004 to 20% in the years 2008 – 2012) and UC-SCs (from 6% per year during 2000 – 2004 to 7% per year during 2008 – 2012) have been increased. The number of published papers in the field of UC-SCs has increased from approximately 7000 articles between 2000 and

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Article highlights.

- The abundance, accessibility and differentiation potential of umbilical cord (UC)-stem cell populations made them a promising source of stem cells for research and clinical applications, including transplantations.
- The future of UC blood stem cell therapy extends beyond conventional transplantation into regenerative medicine, as stem cells may become an important resource for regeneration of tissue and organs.

This box summarizes key points contained in the article.

2004 to 20,000 between 2008 and 2012 (**Figure 2A and B**). We also found that UC blood (UCB) stem cells (> 70% from UC-SCs) were the most common cell type used. The slope of research infield of Wharton's jelly has increased from 0.8% during 2000 – 2004 to 1.5% during 2008 – 2012, thus showing a dramatic growth, nearly doubled, for these infields of UC-SCs (**Figure 2C**).

The UC connects the fetus to the placenta. The human UC is embryologically derived at Day 26 of gestation. The UC at full term, as a rule, is almost equal to the length of the fetus, that is, ~ 50 cm, but it may be either greatly diminished or increased. The UC is essentially composed of amniotic epithelium, which covers mucoid mesenchymal connective tissue (Wharton's jelly). Sarugaser *et al.* [3] postulated that the mucoid mesenchymal connective tissue was derived from a mesenchymal precursor cell population located within the UC [3,4]. The first isolated fetal stem cells were hematopoietic, derived from human UCB. Thus, cord blood (CB) represents the prototypical fetal stem cell source. UCB contains a heterogeneous mixture of stem and progenitor cells at different stages of lineage commitment (mononuclear fraction of UCB cells) [5,6]. UCBMSCs have several advantages over the other stem cell sources. These MSCs have similar cellular, morphological and differentiation properties to bone marrow MSCs but, at the same time, show advantages over bone marrow MSCs that decrease their number and differentiation potential with age. The abundance, accessibility and differentiation potential of UC-SC populations made them a promising source of stem cells for research and clinical applications, including transplantations [7-17].

In vivo studies involving the transplantation of UC and CB-derived stem cells are limited, but encouraging. These cells have been transplanted into animal models of disease and have demonstrated very promising results. Our objective in this review is to summarize the knowledge about UC and CB-derived stem cells and focus mainly on their *in vivo* applications, using novel technologies such as tissue engineering for tissue repair and regeneration in current years.

1.1 Bone/cartilage/tendon

Several novel therapies for bone repair and regeneration have emerged [18,19]. In our study, the bone healing effects of injectable hydrogel with unrestricted somatic stem cells (USSCs) grafted in a rat calvarial model were investigated [20]. Also, bone regeneration was achieved with the nanofibrous polymeric scaffolds and USSCs in rat calvarial defects (**Figure 3**) [21]. These findings suggest the possibility of USSCs as a potent cell source for bone tissue engineering and bone tissue regeneration [20,21].

Emrani and Davies [22] have used human UC perivascular cells (HUCPVCs) to repair tendon damage in a collagenase tendon injury model in immunocompromised rats. Greish *et al.* [23] investigated the effect of human UC-SCs, both mesenchymal and hematopoietic ($CD34^+$), in the treatment of arthritis. The purpose of these studies was similar to Liu *et al.* [24], who observed that control mice exhibited a marked mononuclear cell infiltration, severe synovitis, pannus formation and bone erosion, while the majority of joints from mice injected with UCMSCs had normal morphology with a smooth articulation cartilage surface and an absence of inflammatory cell infiltrate and pannus formation. Also, studies have demonstrated the potential of scaffolding to enhance articular cartilage repair in both *in vitro* and *in vivo* [25,26].

1.2 Cardiovascular tissues

Cortes-Morichetti *et al.* examined the feasibility of a collagen matrix seeded with human UCB-derived stem cells (hUCBSC) and their engraftment onto infarcted ventricles [27]. Henning and his group [28] carried out similar *in vitro* experiments and confirmed that cord blood-mononuclear cells (CB-MNCs) are attracted to ischemic myocardium. Also, they investigated the use of human UCB mononuclear progenitor cells for the treatment of rats with induced acute myocardial infarction (MI). Interestingly, Hu *et al.* [29] also obtained similar results with respect to myocardial contractility, angiogenesis and remodeling processes in infarcted rat heart after CBMNC injection. Ma *et al.* reported on the capacity of UCB mononuclear cells to migrate to the heart of nonobese diabetic/severe combined immune-deficient mice with induced MI [30]. A large animal study by Kim *et al.* demonstrated similar results [31] – by using a porcine-induced MI model, UCB somatic stem cells were injected directly into the infarcted tissue. Similarly, 4 weeks after transplantation, reduction of the left ventricular dilation and improvement of the cardiac function were reported by Hirata *et al.* [32]. Ghodsizad *et al.* [33] have applied an alternative somatic cell type, human CB-derived USSCs in a porcine model of acute MI. Also Ghodsizad *et al.* [34] examined the cardiomyocyte metabolism and the role of high-energy phosphates at the marginal infarct. Weiss [35] studied Wharton's jelly from UC for their long-term therapeutic effect following MI in a rat model to evaluate the effect of donor age [35]. Their results suggested that MSCs given 24 – 48 h after MI have a significant and durable beneficial effect and can improve heart function after intravenous infusion 24 – 48 h after MI, therefore Wharton's jelly cells may be a useful source for off-the-shelf cellular therapy for MI [35]. In 2005, the first

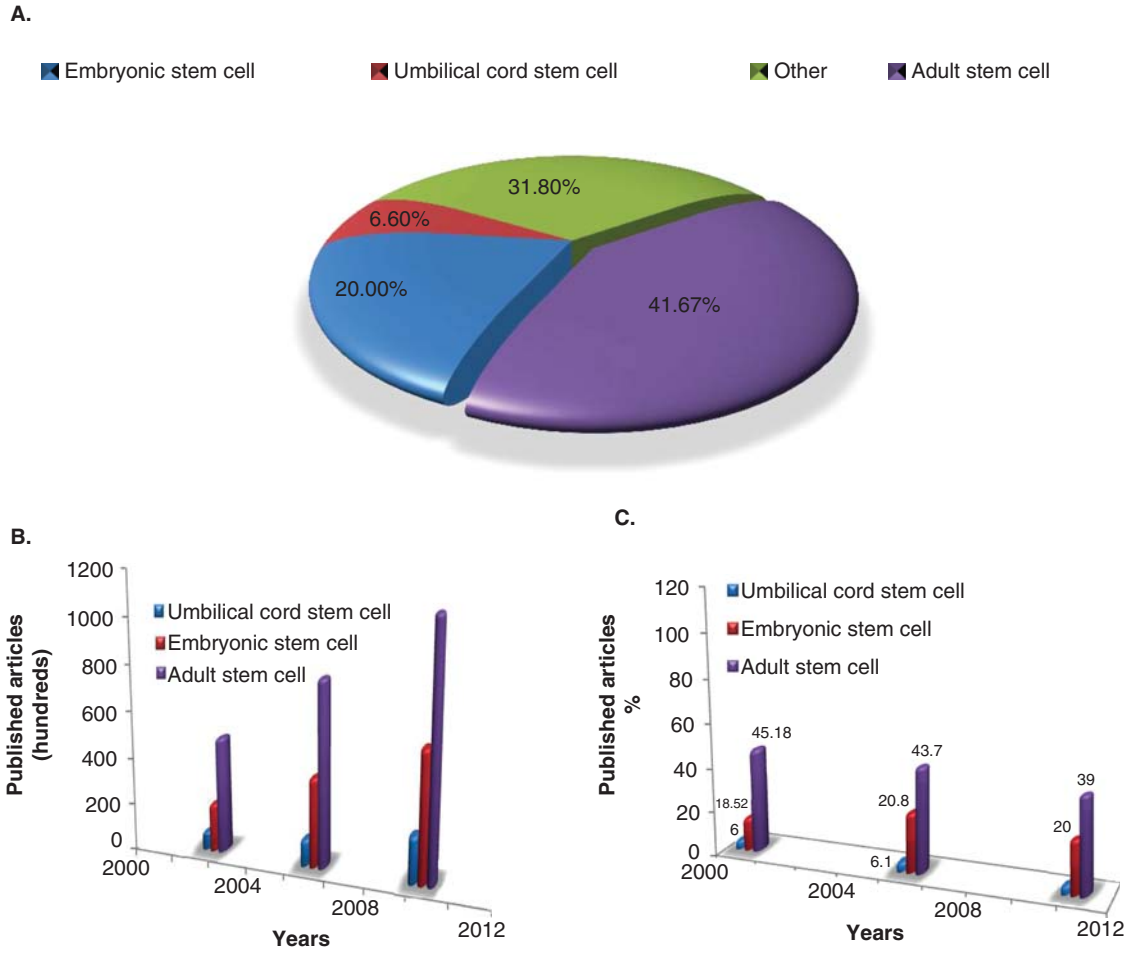

Figure 1. The number of published papers infield of stem cells in recent years from 2000 to 2012. A. The percentage of published articles (%) infield stem cells from 2000 to 2012. **B.** The number of published articles infield stem cells from 2000 to 2004/2004 to 2008 and 2008 to 2012. **C.** The percentage of published articles infield stem cells from 2000 to 2004/2004 to 2008 and 2008 to 2012.

results were related to fabrication of living patches engineered from Wharton's jelly (WJ) MSCs and endothelial progenitor cells (EPCs) [36]. One year later, in 2006, the preliminary results reported for living autologous heart valves based on WJ-MSCs [36,37]. In this study, biologically active heart valve leaflets were engineered using prenatally available human UC-derived progenitor cells as the only cell source. WJ-MSCs and UCB-derived EPCs were subsequently seeded on biodegradable scaffolds and cultured in a biomimetic system under biochemical or mechanical stimulation or both. Depending on the stimulation, the leaflets showed mature, layered tissue formation with functional endothelia and extracellular matrix production comparable with that of native tissues. This demonstrates the feasibility of heart valve leaflet fabrication from prenatal UC-derived progenitor cells as a further step in overcoming the lack of living autologous replacements with growth and regeneration potential for the repair of congenital malformation [36,37]. Semenov and Breymann [38] developed a myocardial patch to use in the repair of MIs or to slow down tissue damage and improve long-term heart function. Myocardial patches based on WJ-MSCs incorporated in three-dimensionally aligned microfibers desired for potential treatment of MIs and improvement of long-term cardiac tissue functions have been described [39]. Turner and Fauza [40] engineered biologically active heart valve leaflets using prenatally available human UC-derived progenitor cells as the only cell source. Sodian *et al.* [41] described the use of cryopreserved UCB-derived $CD133^+$ cells as a single cell source for the tissue engineering of heart valves. Kadner *et al.* [42] evaluated cells isolated from human UC artery and vein, and whole cord as alternative autologous cell sources for cardiovascular tissue engineering. Also, they investigated EPC from UCB as a source for cardiovascular tissue engineering [42]. Schmidt *et al.* [43] investigated the functionality of tissue-engineered living blood vessels (TEBV) with endothelia generated from

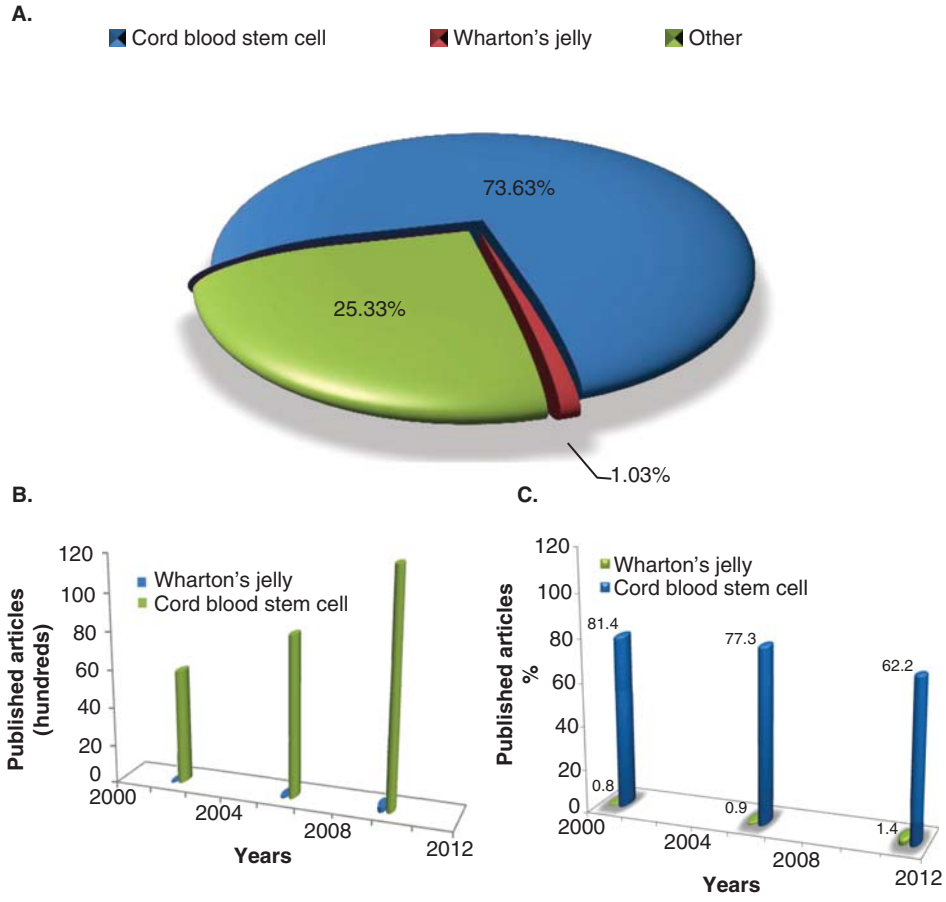

Figure 2. The number of published papers infield of umbilical cord stem cells in recent years from 2000 to 2012. A. The percentage of published articles (%) infield umbilical cord stem cells from 2000 to 2012. **B.** The number of published articles infield umbilical cord stem cells from 2000 to 2004/2004 to 2008 and 2008 to 2012. **C.** The percentage of published articles infield umbilical cord stem cells from 2000 to 2004/2004 to 2008 and 2008 to 2012.

human UCB-derived EPCs. Their results indicate that TEBV with tissue architecture and functional endothelia similar to native blood vessels can be successfully generated from human UC progenitor cells (**Figure 4**) [43]. The CB-derived MSCs were also suggested for the treatment of hind limb ischemia [44].

1.3 Cornea

Studies showed that the UC epithelium expressed a cytokeratin pattern, which is similar to human epidermis. Nichols *et al.* [45] and Harris *et al.* [46] have used CB stem cells as a viable therapeutic modality for ocular surface disease, and as a source of tissue for ocular surface reconstruction. Other investigators have demonstrated that MSCs are also capable of reconstituting the cornea in a rat model [47]. UC serum (UCS) contains many neurotrophic factors; it can also be useful for the treatment of patients with neurotrophic keratitis [48,49]. Oh *et al.* [50] evaluated the effect of UCS eye drops on corneal wound healing in a mouse model of ocular chemical burn and compared with that of peripheral blood serum (PBS) eye drops or artificial tears (AT). Karamichos *et al.* [51] suggested that cord stem cells could potentially be used as an alternative to human corneal fibroblasts, with a potentially longer life span and minimum-to-no risks for the host tissue/organ. Joyce *et al.* [52] indicated that UCBMSCs are able to 'home' to areas of injured corneal endothelium and that the phenotype of UCBMSCs can be altered toward that of human corneal endothelium cell-like cells. Zickri *et al.* studied to assess the possible effect of hematopoietic stem cell (HSC) therapy (CB collection) on induced diabetic keratopathy in albino rat [53].

1.4 Neural tissues

Transplantation into rat transected sciatic nerve showed that the human UC-Schwann cells maintained their differentiated phenotype *in vivo* after transplantation and contributed to axonal regeneration and functional recovery. This finding indicated that UC-Schwann cells are a viable alternative to native Schwann cells and may be applied to cell-based therapy for nerve injuries [54]. Transplantation of human UCB or UCB-derived cells has been proven to improve neurological

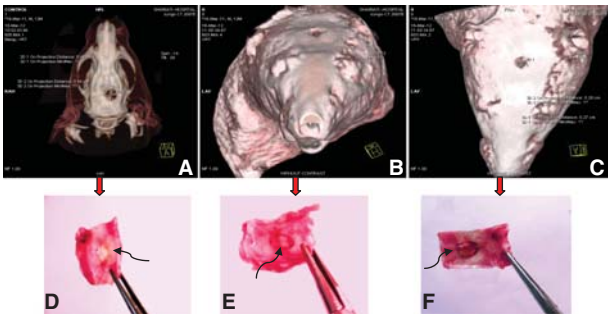

Figure 3. CT analysis and macroscopic images of calvarial defects in rat. Images show regeneration result, after 4 weeks, of bone healing upon implantation of scaffolds in the defect. Control (**A** and **D**); Scaffold alone (**B** and **E**); Scaffold + USSCs pre-cultured *in vitro* (**C** and **F**) [20].

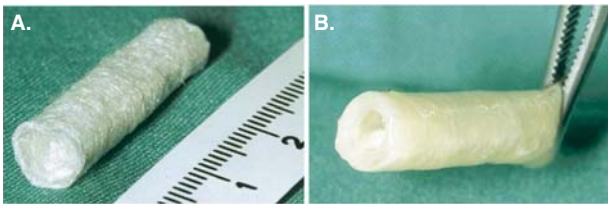

Figure 4. Macroscopic appearance of tissue-engineered blood vessels. Vascular scaffolds from nonwoven polyglycolic acid mesh and poly-4-hydroxybutyric acid before seeding (**A**) and after *in vitro* culturing (**B**) [43].

function in ischemic models [55-57]. Bachstetter *et al.* [58] found that peripherally injecting aged rat brain with the mononuclear fraction of the UCB rejuvenated the aged stem/progenitor cells in the brain and stimulated endogenous stem cells to regenerate new cells. Meier *et al.* [59] showed that transplantation of mononuclear cells from UCB into a damaged brain of a rat model did facilitate motor neuron recovery [59]. Transplantation of human UCMSCs (hUCMSCs) into the injured spinal cord may have the following functions: compensation for demyelination, removal of inhibition, promotion of axonal regeneration, direction of axons to appropriate targets and replacement of lost cells [60-62]. Kang *et al.* [63] purified MSCs from the UCB and used them to treat a 37-year-old woman with a spinal cord injury. The cells were transplanted at the injured location and results showed the regeneration in the spinal cord at the injured site and patient showed improved sensory perception and mobility. Zhilaia *et al.* [64] hypothesized that combining Taxol with another promising therapy, transplantation of hUCMSCs, might further improve the degree of locomotor recovery [65]. In an adult rat model of stroke, Koh *et al.* [66] intracranially injected undifferentiated hUCMSCs 2 weeks after middle cerebral artery occlusion and observed behavioral improvements as early as 1 week after cell transplantation. Similarly, Ding *et al.* [67] showed functional improvements and the stimulation of angiogenesis after hUCMSC transplantation in stroke-injured adult rats. A few studies also investigated the CB therapeutic potential in neurodegenerative diseases, including Parkinson's disease, amyotrophic lateral sclerosis and Alzheimer's disease (AD) [68-70]. Cell transplantation is a strategy with great potential for the treatment of Parkinson's disease [71,72]. Weiss *et al.* has treated rat models affected by Parkinson's disease with hUCMSCs [73]. MSCs have shown promise in treatment of AD *in vitro* and *in vivo* [74,75]. A Phase I clinical trial (NCT01297218) of using human UCB-derived MSCs for the treatment of AD patients is completed [76]. In addition, comprehensive studies of neurotrophic factors secreted from UCB will reveal the underlying mechanisms of neuroprotection by transplanted UCB in neural injuries. Fresh or cryopreserved UCB is undoubtedly a good candidate for stem cell-based therapy and has a great potential in clinical application.

1.5 Skin

Several novel therapies for skin repair and regeneration have emerged. Stem cell-based therapies are attractive candidates in regenerative medicine to treat skin injuries [65]. The studies demonstrate that UCB-derived MSCs contribute to skin tissue regeneration *in vivo* and may be an ideal cell source for therapy of skin epithelial tissue injury, including burns [77,78].

Azari *et al.* investigated the effects of transplanted WJ-MSCs of caprine UC on cutaneous wound healing process in goat [79]. Zhang *et al.* prepared a mixture of hUCMSCs, Wharton's jelly and skin microparticles, and transplanted it to 10-mm diameter, full-thickness, mid-dorsal, excisional skin wounds of mice [80]. Yoo *et al.* [81] isolated and successfully expanded UC-derived MSCs (UC-MSCs) from the Wharton's Jelly. To confirm whether the cells could induce hair follicle instead of dermal papilla, they transplanted with outer root sheath cells (ORSCs) in athymic nude mice's inner dermis, where cells underwent proliferation and differentiation [81]. Fibrin was used as a delivery vehicle for HUCPVC for skin regeneration. Results showed that HUCPVCs accelerate early wound healing in full-thickness skin defects, and thus, represent a putative source of human MSCs for use in dermal tissue engineering [82]. Liao *et al.* [83] demonstrated that USSCs could be induced to express genes, which hallmark keratinocyte differentiation. In mice with full-thickness excisional wounds, a single intradermal injection of USSCs at a 1-cm distance to the wound edge resulted in significantly accelerated wound healing [82]. Our studies [84-86] revealed the great efficacy of different nanofibrous and porous scaffolds loaded with USSCs as skin grafts for treating the acute full-thickness skin wounds in a rat model (**Figure 5**). These findings suggest a great potential of the scaffolds loaded with USSCs as efficient skin grafts for the treatment of acute full-thickness skin wounds [84-86].

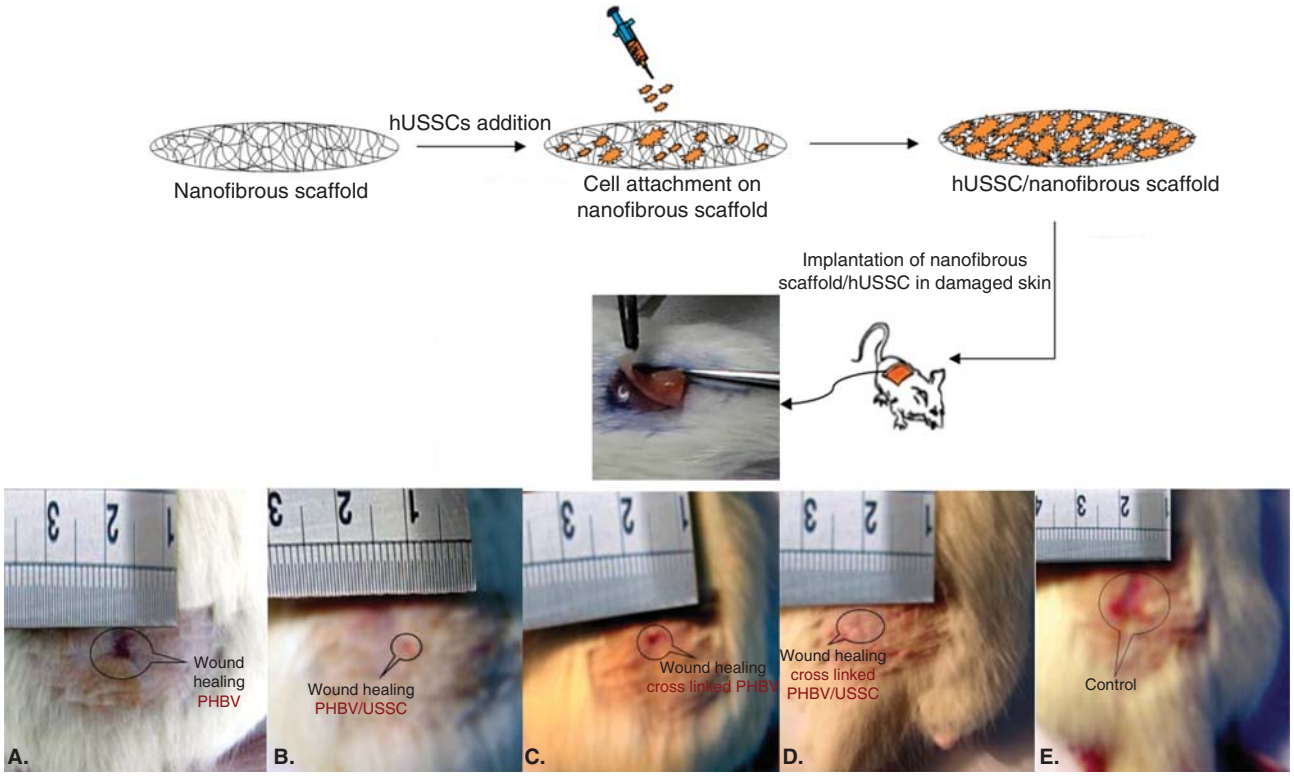

Figure 5. Wound healing at the day 21 after grafting. A. The nanofibrous PHBV scaffold without USSCs. **B**. The nanofibrous PHBV scaffold with USSCs. **C**. The chitosan cross-linked nanofibrous PHBV scaffold without USSCs. **D**. The chitosan cross-linked nanofibrous PHBV scaffold with USSCs. **E**. The control [85].
USSCs: Unrestricted somatic stem cells.

1.6 Liver

Transplanted CB-derived MSCs were able to reduce blood glucose levels and increase survival in mouse models of type 1 and 2 diabetes mellitus; in other model of diabetes, CB cell infusion also improved renal abnormalities and neuropathy caused by diabetes, suggesting a regenerative action in renal parenchyma and nerves [87,88]. Haller *et al.* conducted a pilot study to document the safety and potential efficacy of autologous CB infusion in subjects with type 1 diabetes [89]. Shi *et al.* [90] aimed to evaluate the effects of human UCBMSC (hUCBMSC) transplantation in acute hepatic necrosis (AHN). Ghodsizad *et al.* [91] evaluated the impact of transplanted human multipotent CB-derived USSC on liver regeneration and identified the underlying mechanisms in an ovine model. The studies revealed that transplanted USSC differentiate into hepatocytes and produce human albumin. Transplantation of USSC enhances the number of viable hepatocytes in liver disease by differentiation and opens new therapeutic perspectives [91].

1.7 Other tissues

The application of hUCBMSCs in treating other tissues has been reported in a lot of studies. Haller *et al.* [92] showed the potentiality of autologous UCB transfusion for type 1 diabetes. Chang *et al.* found that hUCBMSCs transplantation significantly delayed the development of proteinuria, decreased anti-dsDNA, alleviated renal injury and prolonged the life span [93]. Therapeutic effects demonstrated that this preclinical study supports further exploration of the possibility to use hUCBMSCs from mismatched donors in lupus nephritis treatment. Sun *et al.* [94] explored if hUCBMSCs transplant may improve symptoms and biochemical values in patients with systemic lupus erythematosus. Chang *et al.* [95] examined whether intratracheal or intraperitoneal transplantation of hUCBMSCs can attenuate hyperoxia-induced lung injury in immunocompetent newborn rats. These findings suggest that the administration of hUCBMSCs might be a possible candidate for the new therapeutic modality for the hyperoxia-induced neonatal lung diseases, such as clinical bronchopulmonary dysplasia [95]. CBMSCs appear to be comparable to MSCs obtained from adult bone marrow in the ability to express phenotypic markers of airway epithelium and to participate in airway remodeling *in vivo* [96]. Tu *et al.* [97] studied the protective effects of hUMSCs on lung fibrosis and normal lung growth in newborn rats [97]. Stem cell-based therapy has significant potential to treat various diseases, including primary and metastatic cancers. Ayuzawa *et al.* [98]

showed that un-engineered human and rat UCMSCs significantly attenuated the growth of multiple cancer cell lines *in vivo* and *in vitro* through multiple mechanisms. A recent animal study demonstrated that CB stem cells might have clinical utility to repair inner ear damage and restore hearing [99]. Human CB stem cells, when intravenously injected into immunodeficient mice made deaf by exposure to kanamycin, high-intensity noise or a combination of these insults, migrated and engrafted into the cochlea of the deaf mice and the levels of engraftment correlated with both the severity of damage and the treatment dose. This study has led to discussion and enthusiasm to translate these promising findings into a clinical trial to investigate autologous CB infusions for childhood hearing damage [99].

2. Expert opinion

The most exciting area of CB stem cells is in their biologic potential. Stem cells provide a powerful research and clinical tool for pharmacology, genomics, cell therapy and tissue engineering. Research is currently underway in a variety of new studies of UC-MSCs application. Each type of stem cells (embryonic, CB, adult) has its advantages and drawbacks when considered for potential clinical applications. UCB offers an alternative source of stem cells with both research and clinical advantages over other sources of stem cells. With the global birth rate exceeding 140 millions/year, UCB can be considered as one of the most abundant sources of stem cells. Also unlike ES cells, UCB stem cells collection is not associated with complicated ethical, religious or political concerns, which makes them more appealing to use in the clinical practice. UCB stem cells also show a number of advantages over adult stem cells sources like bone marrow. In addition to the non-invasive collection procedure, UCB stem cells show higher proliferating potential and longer telomeres than other adult stem cells. UCB transplantation was shown to be associated with a lower risk of infection transmission in comparison with bone marrow transplantation. On the other hand, the low number of stem cells per CB unit represents a limitation that is associated with delayed engraftment of these cells into host targeted tissues. However, this obstacle has been tackled with the possibility of combining multiple CB units in order to increase the final transplanted cell dose resulting in improved engraftment and survival of the transplanted cells. Considering that acquiring UCMSCs is a non-invasive technique, these cells would appear to be the ideal candidates for clinical cell-based therapies. It would appear to be promising news for use in future *in vivo* studies and consequently clinical trials for tissue repair therapies. The future of UCB stem cell therapy extends beyond conventional transplantation into regenerative medicine, as stem cells may become an important resource for regeneration of tissue and organs.

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Declaration of interest

The author reports no declarations of interest. The author alone is responsible for the content and writing of the paper.

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