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REVIEW

Perinatal stem cells: A promising cell resource for tissue engineering of craniofacial bone

Jia-Wen Si, Xu-Dong Wang, Steve GF Shen

Jia-Wen Si, Xu-Dong Wang, Steve GF Shen, Department of Oral and Craniomaxillofacial Science, Shanghai Ninth People's Hospital College of Stomatology, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China
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Correspondence to: Xu-Dong Wang, DDS, MD, Department of Oral and Craniomaxillofacial Science, Shanghai Ninth People's Hospital College of Stomatology, Shanghai Jiao Tong University School of Medicine, 639, Zhizaoju Road, Shanghai 200011, China. xudongwang70@hotmail.com
Telephone: +86-21-23271251
Fax: +86-21-53072423
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Abstract

In facing the mounting clinical challenge and suboptimal techniques of craniofacial bone defects resulting from various conditions, such as congenital malformations, osteomyelitis, trauma and tumor resection, the ongoing research of regenerative medicine using stem cells and concurrent advancement in biotechnology have shifted the focus from surgical reconstruction to a novel stem cell-based tissue engineering strategy for customized and functional craniofacial bone regeneration. Given the unique ontogenetical and cell biological properties of perinatal stem cells, emerging evidence has suggested these extraembryonic tissue-derived stem cells to be a promising cell source for extensive use in regenerative medicine and tissue engineering. In this review, we summarize the current achievements and obstacles in stem cell-based craniofacial bone regeneration and subsequently we address the characteristics of various types of perinatal stem cells and their novel application in tissue engineering of craniofacial bone. We propose the promising feasibility and scope of perinatal stem cell-based craniofacial bone tissue engineering for future clinical application.

Key words: Craniofacial bone regeneration; Bone tissue engineering; Extraembryonic tissue; Perinatal stem cells

Core tip: Given the unique ontogenetical and cell biological properties of perinatal stem cells, emerging evidence has suggested these extraembryonic tissue-derived stem cells to be a promising cell source for extensive use in regenerative medicine and tissue engineering. In this review, we summarize the current achievements and obstacles in stem cell-based craniofacial bone regeneration and subsequently we address the characteristics of various types of perinatal stem cells and their novel application in tissue engineering of craniofacial bone. We propose the promising feasibility and scope of perinatal stem cell-based craniofacial bone tissue engineering for future clinical application.

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INTRODUCTION

The craniofacial bone has an essential role in supporting the adjacent soft tissues, providing anchorage for dental structures, maintaining structural stability for many physical functions and composing the esthetics of the human body. Craniofacial bone defects resulting from various conditions, such as congenital malformation, trauma, osteomyelitis and tumor resection, often lead to large psychomedical burdens as well as difficult reconstructive challenges for both patients and craniofacial surgeons[1-5]. Current treatments for such skeletal defects often require invasive and technically challenging operations such as alloplastic reconstruction, bone grafting from various anatomic areas like the iliac crest and fibula and microvascular free-flap techniques[3,4,6-8]. While these procedures have been proven to be reliable and effective, they also result in secondary donor site defects, associated intra- and post-operative complications and extended hospitalization. Furthermore, these techniques were largely limited by the scarcity of donor bone graft volume and patient physical conditions and struggled to restore pre-operative form and function. Suggested by recent clinical studies, stem cell-based bone tissue engineering has been recognized as a promising strategy for both aesthetic and functional reconstruction of craniofacial bone defects[9-14].

To date, several stem cell sources, such as adult mesenchymal stem cells or mesenchymal stromal cells (MSCs), embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), have displayed promising osteogenic potential *in vivo* and *in vitro* and thus have been proposed as a potential cell source for bone tissue engineering[9,11-13,15,16]. However, the limitations associated with these stem cell sources are also significant[13,17-20]. In the last decade, the list of putative human stem cell sources was amended to include human perinatal extraembryonic tissues, such as amniotic fluid, fetal membranes (amnion and chorion) and umbilical cord[21-23]. Due to their unique ontogenetic relationship to fetal development, the extraembryonic perinatal stem cells represent an intermediate cell type which has recently been described to combine qualities of both their adult stem cell counterparts and ESCs and possess immunoprivileged characteristics, as well as a broad multipotent plasticity[24-29]. Most importantly, these cells, simply isolated from extraembryonic tissues which are normally discarded after birth, effectively avoid ethical issue involvement. All these attractive characteristics make perinatal stem cells a promising and noncontroversial source of stem cells for extensive use in craniofacial bone tissue engineering (CBTE).

In the present review, we summarize the current research progress on stem cell-based craniofacial bone regeneration and subsequently we address the characteristics of various perinatal stem cells and their novel application in CBTE.

CRANIOFACIAL BONE TISSUE ENGINEERING AND STEM CELLS

Craniofacial bone tissue engineering

As an alternative to surgical reconstruction, multidisciplinary developments in cell and molecular biology, developmental biology, materials science and bioengineering promoted the tissue engineering approach, which was composed of stem/progenitor cells, biocompatible scaffolds and biochemical signals, to regenerate large tissue defects[30]. The ongoing tissue engineering strategy offers several potential benefits, including the avoidance of secondary donor site defect, reduction of hospitalization and medical burdens and most importantly, the ability to closely restore the normal anatomic structure and function. Among the variety of current tissue regenerative indications based on the tissue engineering strategy, craniofacial bone defect is particularly suited to be tissue engineered. In fact, stem cell-based bone tissue engineering has already entered many preclinical or clinical applications in the craniofacial region.

Adult MSC-based craniofacial bone tissue engineering

Currently, one of the most well-defined and utilized stem cell types in CBTE is the adult MSCs. These stem cells have been isolated and identified from various tissues such as bone marrow, adipose, muscle, dental pulp and periodontal ligament[9,11,12,14,31,32]. In 2001, Shang *et al*[33] showed augmented healing of sheep cranial defects with calcium alginate gel containing autologous bone marrow-derived MSCs (BMSCs). In 2004, Cowan *et al*[34] first demonstrated that hydroxyapatite-coated polylactic-co-glycolic acid scaffolds seeded with adipose-derive MSCs (AMSCs) promoted bone regeneration of critical-size calvarial defects using a rodent model[34]. More recently, a stem cell-based temporomandibular joint (TMJ) condylar bone graft using a tissue engineering strategy was reported, which suggested the possibility of generating an entire articular condyle in the same shape and dimensions of a human TMJ *in vivo*, with both cartilage and bone layers from a single population of MSCs[35]. These observations were constantly supported in various craniofacial defect models of mouse, rabbit and canine, with the utilization of different MSC and biomaterial scaffolds[9,11,12,14,36-42]. In clinical experiments, autologous BMSCs were seeded onto bioscaffolds and transplanted to repair the mandible or alveolar defect in patients and showed satisfied ossification at the regenerated site in terms of both esthetic and functional outcome[10,43-45]. In 2009, Mesimäki *et al*[46] reported the first use of a microvascular custom-made ectopic bone flap developed from a preformed titanium cage filled with autologous AMSCs, β-tricalcium phosphate (β-TCP) granules to reconstruct a maxillary defect. Most recently, Thesleff *et al*[47] described a novel method to reconstruct critical-sized calvarial defects of adult patients using autologous AMSC and β-TCP granules, providing evidence that AMSCs combined with β-TCP can be used

to regenerate calvarial bone, with favorable clinical results. Although there have been many reports of preliminary success using adult MSCs both in the laboratory and clinic for craniofacial bone regeneration, these stem cell sources are still significantly limited by their scarcity, invasive cell collection and cell aging[15,16,19,48].

Pluripotent stem cell-based craniofacial bone tissue engineering

After the revolutionary discovery and characterization of ESCs and iPSCs, further advances have been made towards applying bone tissue engineering methods with these promising pluripotent stem cells[15,16,19,20,49]. Harkness *et al*[50] reported a subpopulation of fibroblast-like ESCs which showed up-regulation of osteogenic specific markers and production of extracellular mineralization when cultured in osteogenic induction medium. The implantation of these cells in a critical-sized calvarial defect of immune deficient mice resulted in promoted new bone formation and partial repair of the calvarial defect[50]. More recently, Ye *et al*[13] demonstrated de novo osteogenesis of iPSCs within a critical-sized calvarial bone defect[13]. However, the application of ESCs and iPSCs in craniofacial regeneration are still at a preliminary stage and significantly limited by controversial political and ethical concerns, as well as genomic instability, tumorigenesis and immune rejection[16-18]. The drawbacks of these stem cell types may restrict their utility and performance in further clinical practice, prompting increasing interest in alternative stem cell sources for bone tissue engineering.

PERINATAL STEM CELLS

Perinatal stem cell research has been attracting mounting interest worldwide in recent years. Various populations of stem cells, most of which are comprised within the category of mesenchymal stem cells, have been isolated from different extraembryonic-associated tissues.

Amniotic fluid-derived stem cells

Amniotic fluid (AF) is the nourishing and protective liquid located within the fetal sac throughout the gestational stage which contains heterogeneous cells originating from embryonic and extraembryonic tissues[51,52]. Previously, cells obtained from AF were mostly used for diagnostic purposes, such as sex determination, detection of fetal infections and genetic diseases. During the last decades, different groups of researchers have provided evidence that human amniotic fluid could be a pool of stem cells. In 2003, Prusa *et al* demonstrated that a distinct subpopulation of cells expressing OCT4, a key transcript factor for pluripotent human stem cells and preventing differentiation of stem cells, can be found in human amniotic fluid. In the same year, In't Anker *et al*[53] demonstrated that human amniotic fluid contained a fibroblast-shaped cell population positive for mesenchymal markers such as CD90, CD105, CD73 and CD166 but negative for the hematopoietic markers such as CD45, CD34 and CD14[53]. Notably, De Coppi *et al*[54] successfully isolated a multipotential subpopulation of stem cells in the amniotic fluid by fluorescence-activated cell sorting for c-kit positive cells. These amniotic fluid-derived stem cells (AFSCs) maintain a round shape for 1 wk after isolation and begin to change to a fibroblastoid morphology from the second week. Long term culture shows a high self-renewal capacity of these cells with > 300 population doublings, far exceeding Hayflick's limit. The doubling time of the undifferentiated cells is noted to be 36 h, with little variation during passaging. Analysis of stem cell markers shows that the AFSCs express pluripotent markers SSEA4 and OCT4, as well as typical mesenchymal markers, but they did not express the full complement of pluripotent markers, such as SSEA1, SSEA3, TRA1-60 or TRA1-81, indicating that AFSCs are not as primitive as ESCs and yet maintain greater potential than most adult MSCs[54-56]. Later, the existence and multi-differentiation capabilities of AFSCs into cells and tissues from all three embryonic germ layers was widely confirmed by various independent reports[54,57-63]. Promising results in terms of structural and functional outcomes highlight the true clinical potential of AFSCs in cell-based therapies and tissue engineering perspectives.

Amnion-derived stem cells

The amniotic membrane is the innermost fetal layer of the placenta which lines the amniotic cavity and assures the normal growth and development of the fetus during gestation. Normally, two types of stem cells can be isolated from the amniotic membrane through mechanical separation and the subsequent enzymatic digestion, namely amniotic epithelial cells (AECs) and the amniotic mesenchymal stem cells (AMMSCs)[64]. What makes these cells especially attractive is that large amounts can be isolated from an uncontroversial material that is usually discarded after birth. AECs, developing from the central region of the epiblast, build a single layer adjacent to the amniotic fluid and display a cobblestone-like epithelial morphology[64,65]. While AECs reside in the innermost layer of the amnion, AMMSCs differentiated from somatopleuric mesodermal cells reside in the stromal matrix of the amniotic membrane and exhibit a fibroblastoid morphology[66-68]. Given their different ontological and cell biological characteristics, subpopulations from both cell types have been confirmed to express a wide range of pluripotency markers, such as OCT4, SOX2, SSEA4, SSEA3, as well as typical mesenchymal markers[65-70]. Further *in vitro* and *in vivo* studies confirmed their multilineage differentiation potential into cells derived from all three germ layers, such as neuron-like cells, cardiomyocytes, chondrocytes, osteocytes and hepatocytes[69,71-81]. Most importantly, the immunomodulatory capacity and immunoprivileged status of amnion-derived stem cells make them a promising candidate for allogeneic transplantation and stem cell based therapies[2,25-27,82-91]. However, standardized collection, quality control and further preclinical and clinical research are still needed before safe amnion-derived stem cell banking products can be achieved[92].

Chorion-derived mesenchymal stem cells

The chorionic membrane of human term placenta is a rich source of stem cells from which mesenchymal stem cells from chorionic villi and chorionic plate can be isolated[24,93]. Notwithstanding the potential contamination of decidual maternal stem cells suggested by many studies of term chorionic cells with both fetal and maternal origin, or even pure maternal origin cells only, previous studies of these chorion-derived mesenchymal stem cells (CMSCs) have been focused on primary isolation and limited cell characterization[24,66]. Like their stem cell counterparts from the placenta, CMSCs participate in placental tissue generation, maintenance, repair and possess a intermediate phenotype of adult MSCs and pluripotent stem cells[93-95]. *In vitro*, the CMSCs have been reported to be more primitive than adult MSCs with evidence of greater self-renewal and potential to differentiate beyond mesenchymal cell lineages to other lineages such as hepatocyte-like cells and neuron-like cells[24,93,95-98]. *In vivo*, the CMSCs have recently been reported to have a therapeutic effect on liver injury and osteogenesis imperfecta through not just direct hepatocyte and osteocyte differentiation, but also secretion of cytokines and inhibition of donor cell apoptosis[97,98]. Very recently, Jones *et al*[99] reported that CMSCs isolated from first trimester but not term human placenta accelerated tissue repair in dermal excision skin wounds and improved bone quality and plasticity in osteogenesis imperfecta of mice. Interestingly, the first trimester CMSCs showed an earlier state of stemness, such as smaller size, faster kinetics, unique formation of embryoid bodies and higher expression levels of NANOG, SOX2, c-MYC and KLF4, than its term isolated counterparts. However, collection of CMSCs in the first trimester is technically challenging and usually requires early termination of pregnancy, an ethical obstacle to clinical applications.

Umbilical cord-derived mesenchymal stem cells

The umbilical cord (UC) is an elastic cord that connects the fetus to the placenta during pregnancy. Anatomically, the UC consists of two umbilical arteries (UA) and one umbilical vein (UV) embedded in a mucous connective proteoglycan-rich matrix called Wharton's jelly (WJ). Since more than a decade ago when two independent teams reported their successful isolation of mesenchymal like cells from porcine and human umbilical cord respectively[100,101], there has been increasing interest in studying the potential of umbilical cord-derived mesenchymal stem cells (UCMSCs) for regenerative medicine. Generally, UCMSCs have been reported to be isolated from different parts of the UC such as UA, UV, WJ, umbilical-lining membrane and umbilical cord blood (UCB)[102]. Based on the optimized methods to isolate, culture and cryopreserve human UCMSCs, a human UC-MSC bank complying with good manufacturing practices has been established[103]. Given the controversy that exists on whether UCB or umbilical vessel-derived MSCs can be isolated, MSCs isolated from these various parts of UC have been shown to resemble adult BMSCs while retaining some specific characteristics. *In vitro*, UCMSCs appear with a fibroblastoid morphology and display a greater expansion capacity and faster doubling time than adult BMSCs. Their morphology and proliferative characteristics did not change even after 30 passages[100,101]. These cells consistently express typical mesenchymal markers as well as α-smooth muscle actin and low levels of pluripotency markers, such as Oct4, Sox2 and Nanog[100,104,105]. Moreover, UCMSCs express a lower level of HLA-ABC than BMSCs and were negative for CD31, CD34, CD45, HLA-DR, CD80 and CD86[106]. *In vitro* and *in vivo* studies confirmed their multi-differentiation potential of mesodermal lineages, such as osteocytes, chondrocytes and cardiomyocytes, as well as other lineages such as neuron-like cell and hepatocytes[100,107-111]. Most importantly, UCMSCs possess immunomodulatory effects *in vitro* and *in vivo* and have been shown to be well tolerated in allogeneic transplantation experiments[28,106,112]. Promising results of preclinical and clinical studies using UCMSCs for treatment of liver fibrosis, systemic lupus erythematosus, Sjogren's syndrome and GVHD have been reported which will further promote the therapeutic application of UCMSCs in cell-based regenerative medicine[112-115].

APPLICATION OF PERINATAL STEM CELLS IN CRANIOFACIAL BONE TISSUE ENGINEERING

Due to their same ontogenetic origin, perinatal stem cells isolated from different extraembryonic tissues possess similar phenotypic and functional properties. In fact, AFSCs, AECs, AMMSCs, CMSCs and UCMSCs have been shown to exhibit osteogenic differentiation capacity both *in vitro* and *in vivo*[77,93,97,116-119]. In limited comparative studies, perinatal stem cells such as AFSCs and UCMSCs have been shown to display lower basal levels of bone-related genes, higher proliferation rate and much later senescence than BMSCs, resulting in a delayed but robust osteogenic differentiation capacity, which render them a promising candidate for cell banking and stem cell-based bone tissue engineering[120-122].

In face of the mounting clinical demand and suboptimal techniques for craniofacial skeleton reconstruction, perinatal stem cells may be particularly useful for autologous or allogeneic CBTE for newborns and children and may also be used for adult patients after banking at later stages of life (Figure 1). Although preclinical applications of perinatal stem cells in craniofacial bone regeneration are still limited, recent research progress of these cells revealed multiple possibilities for their potential applications in CBTE.

One of the most advanced applications of perinatal stem cells in CBTE was demonstrated by the use of UCMSCs in restoring rat cranial defects. Chen and colleagues investigated the *in vitro* and *in vivo* bone regenerative performance of human UCMSCs and BMSCs with RGD-modified macroporous calcium phosphate cements (CPC), using a critical-sized athymic rat parietal bone defect (8 mm in

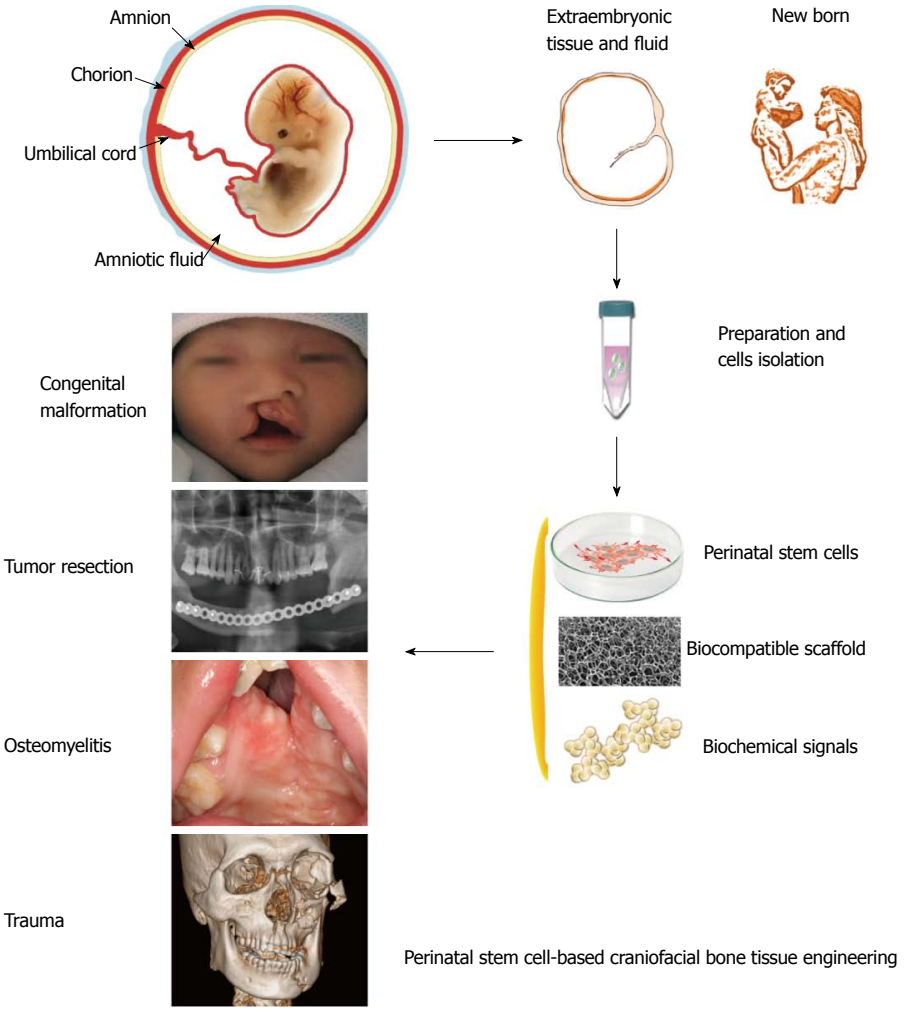

Figure 1 Schematic illustration of the perinatal stem cell-based craniofacial bone tissue engineering. Generally, perinatal stem cells are easily harvested with no harm to the baby or mother and hold a most promising perspective for extensive application in tissue engineering. In the most visionary view, through sophisticated control of perinatal stem cells, biocompatible scaffolds and a signaling system, we will finally be able to bring the perinatal stem cell-based bone tissue engineering strategy to the customized and functional clinical reconstruction of craniofacial bone defects resulting from congenital malformations, osteomyelitis, trauma and tumor resection.

diameter) model[123]. They observed similarly high expressions of osteogenic specific genes and high percentages of live cells and cell density on CPC for UCMSCs and BMSCs. After implantation for 24 wk, the new bone tissue of UCMSC-CPC and BMSC-CPC groups *in vivo* exhibited similarly higher bone mineral density, new bone amount and vessel density compared to the CPC control group. Notably, this observation was in agreement with a former study by Liu *et al*[124] using human UCMSCs and partially demineralized bone matrix for reconstruction of critical-sized parietal bone defects (5 mm in diameter) in athymic rats. Interestingly, Barboni *et al*[125] reported AEC-enhanced bone regeneration using an ovine maxillary sinus augmentation model. Calcium-phosphate synthetic bone substitutes, alone or engineered with ovine AECs, were grafted bilaterally into maxillary sinuses of six adult sheep. After implantation, the scaffold integration and bone deposition are positively influenced by allotransplanted AECs. Sinus explants derived from an AEC-scaffold group displayed a reduced fibrotic reaction, a limited inflammatory response and an accelerated process of angiogenesis compared with the control group. In addition, a direct osteogenic differentiation of ovine AECs *in vivo* was observed at 45 d post operation, suggested by the presence of AECs-derived osteocalcin-expressing osteocytes entrapped within the newly deposited bone matrix. The general concept of perinatal stem cell-based bone tissue engineering has also been validated using ASCs in several craniofacial bone defect models. A commercial magnesium-enriched hydroxyapatite (MgHA)/collagen-based scaffold seeded with or without ovine AFMCs was implanted in the bilateral maxillary sinus of sheep models for up to 90 d. Results showed that application of AFMCs increased new bone deposition and stimulated a more rapid angiogenic reaction[126]. In another study, researchers developed two combined constructs by seeding dental pulp stem cells (DPSCs) and AFSCs onto silk fibroin scaffolds respectively. The AFSCs-scaffold construct as well as DPSC-scaffold construct promoted early bone regeneration in the critical-sized rat parietal bone defects compared with scaffold alone[127]. However, the relative long-term outcome of AFSCs in craniofacial bone repair was still in question and the optimal scaffold composition for this particular application remains to be defined[128,129]. In addition, suggested by most of the discussed studies, perinatal stem cells may play an essential role in new vessel formation in the regeneration site, which indirectly promotes the restoration of craniofacial bone defects[123,125,126,128].

CONCLUSION

The ontological and anatomical origins of stem cells have profound influences on their biological properties and performance in regenerative medicine. Promoted

by the developments in cell and molecular biology, developmental biology and tissue engineering, the unique and advanced properties of perinatal stem cells have been largely unveiled within the last decade: (1) the collection, preparation and application of perinatal stem cells are scarcely involved with ethical issues; (2) most perinatal stem cells are easily harvested and manipulated with no harm to the baby or mother; (3) compared to adult MSCs which decreased in cell number, proliferation ability and differentiation capacities with age, perinatal stem cells are initially available in substantial numbers and exhibit greater proliferative activity than BMSCs, indicating the advantage for rapid expansion and consequent downstream application; (4) with an intermediate multipotency between pluripotent stem cells and adult MSCs, perinatal stem cells do not form a teratoma while maintaining a broad multi-differentiation capacity *in vitro* and *in vivo*; and (5) in terms of their involvement in materno-fetal immunotolerance, perinatal stem cells exhibit low immunogenicity and potentially high immunomodulatory capacity, indicating a clinical prospective of allogeneic cell transplantation. However, the mechanisms underlying the immunoprivileged and immunosuppressive effects of perinatal stem cells have not yet been clearly defined.

Despite the problems researchers still face in translating scientific concepts from the bench to the bedside, these exciting experimental and preclinical achievements from intense research efforts suggest perinatal stem cells may offer a most promising scope and will continue to produce new and exciting progress for the novel cell-based CBTE in the future.

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